FORM-PTO-1390 (Rev. 12-29-99) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER: 012627-019

U.S. APPLICATION NO. (If known, see 37 C.F.R. 1.5): 09/720215

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/DE99/01867	25 June 1999	26 June 1998

TITLE OF INVENTION: MODULARLY CONSTRUCTED RNA MOLECULES HAVING TWO SEQUENCE REGION TYPES

APPLICANT(S) FOR DO/EO/US: Annemarie POUSTKA; Johannes COY

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☒ This is an express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and the PCT Articles 22 and 39(1).
4. ☒ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. ☒ A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. ☒ is transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☒ has been transmitted by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US)
6. ☒ A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. ☐ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
   a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☐ have been transmitted by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☐ have not been made and will not be made.
8. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. ☐ An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. ☐ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 16. below concern other document(s) or information included:

11. ☒ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. ☒ A FIRST preliminary amendment.
    ☐ A SECOND or SUBSEQUENT preliminary amendment.
14. ☐ A substitute specification.
15. ☐ A change of power of attorney and/or address letter.
16. ☐ Other items or information:

U.S. APPLICATION NO. (If known, see 37 C.F.R. 1.50)	INTERNATIONAL APPLICATION NO.	ATTORNEY'S DOCKET NUMBER
09/720215	PCT/DE99/01867	012627-019

17. ☒ The following fees are submitted:	CALCULATIONS	PTO USE ONLY
Basic National Fee (37 CFR 1.492(a)(1)-(5)):		
Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO $1,000.00 (960)		
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO $860.00 (970)		
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO $710.00 (958)		
International preliminary examination fee paid to USPTO (37 CFR 1.482) but all claims did not satisfy provisions of PCT Article 33(1)-(4) $690.00 (956)		
International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(1)-(4) $100.00 (962)		
ENTER APPROPRIATE BASIC FEE AMOUNT =	$ 860.00	
Surcharge of **$130.00 (154)** for furnishing the oath or declaration later than 20 ☐ 30 ☐ months from the earliest claimed priority date (37 CFR 1.492(e)).	$	

Claims	Number Filed	Number Extra	Rate		
Total Claims	26 -20 =	6	X$18.00 (966)	$ 108.00	
Independent Claims	3 -3 =	0	X$80.00 (964)	$ --	
Multiple dependent claim(s) (if applicable)			+$270.00 (968)	$	
			TOTAL OF ABOVE CALCULATIONS =	$ 968.00	
Reduction for 1/2 for filing by small entity, if applicable.				$ 484.00	
			SUBTOTAL =	$ 484.00	
Processing fee of **$130.00 (156)** for furnishing the English translation later than 20 ☐ 30 ☐ months from the earliest claimed priority date (37 CFR 1.492(f)). +				$	
			TOTAL NATIONAL FEE =	$ 484.00	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). **$40.00 (581)** per property +				$	
			TOTAL FEES ENCLOSED =	$ 484.00	
			Amount to be: refunded	$	
			charged	$	

a. ☒ A check in the amount of $ 484.00 to cover the above fees is enclosed.

b. ☐ Please charge my Deposit Account No. 02-4800 in the amount of $_____ to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 02-4800. A duplicate copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

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NAME

30,427
REGISTRATION NUMBER

Patent
Attorney's Docket No. 012627-019

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of	)	
	)	
Annemarie POUSTKA et al.	)	
	)	
Application No.: Unassigned (Corresponds to PCT/DE99/01867)	)	Group Art Unit: Unassigned
	)	
International Filing Date: 25 June 1999	)	Examiner: Unassigned
	)	
For: MODULARLY CONSTRUCTED RNA MOLECULES HAVING TWO SEQUENCE REGION TYPES	)	

PRELIMINARY AMENDMENT

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

Prior to examination, please amend the above-captioned application as follows:

IN THE CLAIMS:

Kindly amend the claims as follows:

Claim 3, line 1, delete "or 2".

Claim 4, line 1, change "any one of claims 1 to 3" to --claim 1--.

Claim 5, line 1, change "any one of claims 1 to 4" to --claim 1--.

Claim 6, line 1, change "any one of claims 1 to 5" to --claim 1--.

Claim 7, line 2, change "any one of claims 1 to 6" to --claim 1--.

Claim 9, line 2, delete "or the gene according to claim 8".

Claim 14, lines 1-2, change "any one of claims 9 to 13" to --claim 9--.

Claim 16, lines 2-3, change "any one of claims 1 to 6" to --claim 1--.

Claim 18, line 2, change "any one of claims 1 to 6" to --claim 1--.

Claim 19, line 2, change "any one of claims 1 to 6" to --claim 1--.

20. (Amended) [Use of the RNA molecule according to any one of claims 1 to 6, of the vector according to any one of claims 9 to 13, of the antibody or fragment thereof according to claim 16 or 17, of the antisense RNA according to claim 18 or of the ribozyme according to claim 19 for the production of a] A pharmaceutical preparation for preventing or treating diseases which are connected with a disturbed control of gene expression comprising using the RNA molecule according to claim 1.

21. (Amended) [Use of the RNA molecule according to any one of claims 1 to 6, of the DNA sequence according to claim 7 or a fragment thereof, of the antibody or fragment thereof according to claim 16 or 17, or of the antisense RNA according to claim

18 or a fragment thereof] A method for the diagnosis of diseases which are connected with a disturbed control of gene expression comprising using the RNA molecule according to claim 1.

Claim 22, line 1, change "Use" to --The method-- and delete "20 or".

Claim 23, line 1, change "whose" to --comprising a-- and after "gene" insert --which--.

Claim 25, line 1, delete "or 24".

26. (Amended) A process for the production of a non-human mammal according to [any one of claims 23 to 25] claim 23, [characterized by] comprising the following steps:

(a) [preparation of] preparing a DNA fragment, [in particular a vector,] containing a modified NINTROX gene, the NINTROX gene having been modified by deletion of a homologous sequence and/or insertion of a heterologous sequence[, in particular a selectable marker];

(b) [preparation of] preparing embryonal stem cells from a non-human mammal [(preferably mouse)];

(c) [transformation of] transforming the embryonal stem cells from step (b) with the DNA fragment from step (a), the NINTROX gene in the embryonal stem

cells being modified by homologous recombination with the DNA fragment from (a),

(d) culturing the cells from step (c),

(e) [selection of] selecting the cultured cells from step (d) for the absence of the homologous sequence and/or the presence of the heterologous sequence, [in particular the selectable marker,]

(f) [production of] producing chimeric non-human mammals from the cells from step (e) by injection of these cells in mammalian blastocysts [(preferably mouse blastocysts)], [transfer of] transferring the blastocysts into false-pregnant female mammals [(preferably mouse)] and [analysis of] analyzing the resulting offspring for a change of the NINTROX gene.

REMARKS

Entry of the foregoing amendments are respectfully requested.

Should the Examiner have any questions concerning the subject application, a telephone call to the undersigned would be appreciated.

Respectfully submitted,

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Modularly Constructed RNA Molecules Having two Sequence Region Types

The present invention relates to RNA molecules which are characterized by two sequence region types, namely a first sequence region type which contributes to maintaining the three-dimensional structure of the RNA molecule, and a second sequence region type which is responsible for the specific binding of a ligand. These RNA molecules are preferably useful for the direct control of gene expression. The present invention also provides the DNA sequence derived for the RNA molecules according to the invention and vectors which contain them. In addition, the invention relates to drugs or medicaments and diagnostic compositions which contain the above RNA molecules or vectors, to an antibody specifically recognizing these RNA molecules or to antisense RNA specifically binding to these RNA molecules or ribozymes cleaving these RNA molecules. Furthermore, the invention relates to non-human transgenic mammals and cells obtained therefrom.

Gene expression in eukaryotes is usually regulated via proteins which usually bind specifically to certain regulatory sequences upstream of the gene to be expressed and show a characteristic effect (RNA polymerases, transcription factors, receptors adapted to be activated by hormones, etc.). Only few examples of controlling the gene expression directly via RNA molecules have been known thus far. They include the RNA "XIST" responsible for the inactivation of the entire X chromosome ("X chromosome inactivation specific transcript"), an RNA referred to as

IPW ("imprinted in Prader-Willi syndrome") and RNA H19 which represents a tumor suppressor and is involved in the control of certain development processes. The artificial control of the gene expression has meanwhile been effected by the use of antisense RNAs binding specifically to mRNAs or by the use of catalytically active RNA molecules, what is called ribozymes, which do not only bind specifically to the target RNA but also cleave it thus inactivating it. However, the application possibilities for these antisense RNAs or ribozymes are limited, above all as regards the ligand to be bound and inactivated. This ligand may basically only be an RNA.

Thus, there is a need for providing compounds which can universally detect, and/or inactivate, the most differing target molecules, e.g. DNA, RNA, proteins or low-molecular substances, and are suitable e.g. for controlling gene expression and thus, of course, also for preventing and treating diseases which are accompanied by a disturbed gene expression.

Hence the technical problem of the invention is substantially to provide those compounds which are useful *inter alia* for the prevention or therapy (and also diagnosis) of such diseases.

The solution to this technical problem was achieved by providing the embodiments characterized in the claims.

The inventors could identify an RNA molecule which comprises the above described desired properties. This RNA molecule is encoded by the gene "NINTROX" (No INTROns X-chromosome) which has no introns, is localized on the X-chromosome and codes for no protein. This RNA molecule is part of certain

(relatively long) transcripts of the MeCP2 gene. The MeCp2 gene (methyl-CpG binding protein 2) in Xq28 has a transcript of about 1.8 kb which codes for the MeCP2 protein. The above described RNA is part of relatively long MeCP2 transcripts which also code for the MeCP2 protein but have a different 3'-non-translated region. This 3'-non-translated region is decisive for the MeCP2 gene and its function. The below expression "NINTROX" is synonymous with the above relatively long transcripts of the MeCP2 gene.

The genomic sequence of the human NINTROX gene is shown in figure 1, and the genomic sequence of the murine NINTROX gene is illustrated in figure 2. In figure 3, a sequence comparison was carried out between human and murine sequences. It is obvious therefrom that there are some highly sequence-conserved regions which according to an energy analysis carried out by means of a computer distinguish themselves by a high degree of energy (cf. figure 4).

While the mechanism of action of the above discussed genes effective on the RNA level was fully unclear, the principle of action of such a gene which is described in more detail below could, for the first time, be determined by the analysis of the NINTROX gene. The NINTROX gene contributes essentially to the maintenance of the functions of the CNS, in particular the hippocampus. Defects in this gene result in limited CNS functions which reach as far as mental retardations. Furthermore, the NINTROX gene has an important function in the control of cell proliferation. In this connection, changes in this gene can lead to errors in the control of cell growth, e.g. to cancer. Changes in this gene may result in an increased or reduced DNA methylation. An increased DNA methylation can *inter alia* restrict or prevent

the activity of growth-controlling genes (tumor suppressor genes) and thus result in a generally increased cancer rate. Reduced DNA methylation can lead *inter alia* to an overexpression of genes and thus to a disturbed development of the cell or the whole organism. Further investigations led to the result that the expression pattern of the NINTROX gene is effected in tissue-specific and development-specific manner. The Northern analyses showed an expression in all investigated fetal and adult tissues. No sequence homologies with already known sequences could be detected.

The strategy which led to the identification of this nucleic acid molecule is described below. Based on the systematic analysis of the q28 region of the human X chromosome various expressed sequences could be detected and isolated. By means of these expressed sequences some formerly unknown genes could be identified and characterized according to standard methods, *inter alia* the NINTROX gene on which the present invention is based.

It is of interest that the NINTROX-RNA molecules according to the invention have a modular structure, i.e. they are characterized by the presence of two different sequence region types. While one sequence region permits to maintain the three-dimensional structure and, as follows from a comparison of the sequences from various species (human, hamster, kangaroo, macaque or macaca, orangutan chimpanzee and rat; cf. figure 5), is conserved only in a qualified sense, the second sequence region which is responsible for the specific binding to the target molecule is sequence-conserved. Because of this modular construction of the NINTROX-RNA it is possible to modify it such that its effect is not only limited to the above described control of the gene expression but can be used for a number of

possibilities. In addition to the control of the gene expression it is also possible to modify the structure (e.g. chromatin structure, nuclear scaffold) of chromosomal regions by means of such modular RNA molecules. This offers the formerly unknown possibility of being able to influence the expression of relatively large genomic regions in well-calculated fashion. Thus, certain sequence regions of both modules of the NINTROX gene can be replaced by other sequences or even artificial sequences, so that (a) the interaction of this RNA with other binding partners (RNA, DNA, other macromolecules and low-molecular compounds) or their biochemical reaction (e.g. increase or decrease of the conversion rate) are changed in well-calculated fashion, and therefore the RNA molecule can be adapted in well-calculated fashion to novel tasks, and/or (b) the three-dimensional structure of the NINTROX-RNA can be adapted in well-calculated fashion to special demands. As a result, a partially or fully new function of the NINTROX-RNA molecule according to the invention can be obtained.

Thus, an embodiment of the present invention relates to an RNA molecule which may bind to a ligand and comprises the following sequence regions: (a) a sequence region maintaining the three-dimensional structure of the RNA molecule, and (b) a sequence region for the specific binding of the ligand.

The expression "a sequence region maintaining the three-dimensional structure of the RNA molecule" used herein has the following meaning. Three-dimensional RNA structures are rendered possible by base pairing of various bases within the RNA molecule. In this case, structures such as "stems" or "loops" are formed. Many of these structures yield in this way the overall structure of the RNA molecule. A

sequence change within the RNA molecule may remain without consequences for the spatial structure if the sequence change does not change the base pairings or if the sequence change is compensated by a second sequence change. For example, if the base pairing A-T is destroyed in that the A mutates into G, this mutation can be compensated by another mutation of T into C. Although this changes the sequence, the spatial structure remains the same. As a result, the same RNA structure can be formed by an extremely large number of differing RNA sequences. References to certain RNA structures follow from an analysis of the energy included therein. This analysis can be carried out by means of commercially available computer programs (e.g. "FOLD"; Michael Zuker and P. Stiegler: Optimal Computer Folding of Large RNA Sequences Using Thermodynamics and Auxiliary Information, Nucleic Acids Research (81), 9(1), page 133). The lower the energy content of a certain sequence, the more stable the three-dimensional RNA structures. The analysis of the NINTROX gene showed a conserved distribution of these low-energy structures (figure 4). The base sequence of these RNA regions differs widely with various species, but the energy content is very conserved. In figure 3, these are the sequence regions which are not characterized by a black bar at the margin. This means that the sequence region maintaining the three-dimensional structure of the RNA molecule is not sequence-conserved but energy-conserved. For example, modifications of this sequence region do not orient themselves by the base sequence but by the conservation of the detected energy content.

The expression "a sequence region for the specific binding of the ligand" used herein relates to a sequence region which is such that it can bind specifically the desired ligand. These sequence regions are highly sequence-

conserved. In figure 3, these regions are marked by a black bar at the margin and have a high energy content (cf. figure 4). This tallies with the observation that these sequence regions are not "packed" but oriented outwardly and are responsible for the binding of the ligand, enzymatic reactions or the binding to other RNA or DNA sequences. If the ligand to be bound is an RNA molecule or a DNA molecule, this sequence region will be complementary to a corresponding, sufficiently long segment of the RNA molecule or DNA molecule. If the ligand to be bound is a protein, the sequence region (b) may be partially or fully exchanged, or supplemented, by a DNA sequence which as is known binds specifically the desired protein.

The two above-described sequence types occur several times within the NINTROX-RNA. The exchange or the change of individual ones of such modules enables the well-calculated change of the NINTROX-RNA. In a modification of the module maintaining the three-dimensional structure attention has to be paid to the energy content, so that it maintains a minimum value. The modification of the other sequence region is only subject to minor restrictions even though it is deemed to be sequence-conserved. This region may be omitted fully or partially or may contain insertions. For example, it is also possible to insert sequences into the NINTROX-RNA molecule which have known biochemical properties or bind certain DNA molecules, RNA molecules or proteins. In addition, random sequences of differing length may be introduced into various sites of the NINTROX gene and thereafter selection for specific properties such as biochemical reaction, specific binding, etc., may be carried out.

In a preferred embodiment of the RNA molecule according to the invention the sequence region (a) comprises the sequence regions not marked at the margin in figure 3 or sequences related thereto which also permit the maintenance of the three-dimensional structure of the RNA molecule and differ from sequence region (a) in figure 3. These differences relate to the addition, deletion and/or insertion of bases, at least 80 %, preferably 85 %, and more preferably at least 90 %, of the energy content determined for the sequence of figure (3) being maintained. The original three-dimensional structure is preferably maintained when these changes are introduced.

In a particularly preferred embodiment, the sequence region (b) of the RNA molecule according to the invention comprises the sequences which are illustrated in figure 3 and marked with black bars at the margin.

In another preferred embodiment of the RNA molecule according to the invention, the ligand to be bound is a DNA molecule or a protein or enzyme, e.g. DNA polymerase I. The RNA molecule according to the invention preferably contains a poly(A) sequence at the 3' end, which may contribute to the stability in a desired host cell.

In another preferred embodiment, the RNA molecule according to the invention is used to control the gene expression. For this purpose, the sequence region (b) is modified such that it binds a protein responsible for gene expression or binds to a certain DNA region of the target gene so as to impede or prevent e.g. the attachment of proteins which exert an influence inhibiting or supporting gene expression or also binds directly to the mRNA of the target gene so as to impede or prevent the translation, for example. The person

skilled in the art can readily modify the RNA molecule according to the invention by corresponding modification of sequence region (b) and possibly also of sequence region (a) such that it binds the desired ligand and therefore controls the gene expression to the desired extent.

The present invention also relates to a DNA sequence coding for the RNA molecule according to the invention and to a gene comprising the following features: It contains a promoter which permits the transcription in a desired host cell and a DNA sequence functionally linked therewith and encoding the RNA molecule according to the invention. The gene preferably contains additionally a termination signal and a polyadenylation site.

In a preferred embodiment, the gene according to the invention comprises the sequence shown in figure 1 or 2.

The DNA sequences or genes, coding for the RNA molecule according to the invention, may also be inserted in a vector. Thus, the present invention also comprises vectors containing these DNA sequences or genes. The term "vector" relates to a plasmid (e.g. pUC18, pBR322, pBlueScript), to a virus or another suitable vehicle. In a preferred embodiment, the sequence coding for the DNA molecule according to the invention is functionally linked in the vector with regulatory elements which permit its expression in prokaryotic or eukaryotic host cells. In addition to the regulatory elements, e.g. a promoter, such vectors typically contain a replication origin and specific genes which permit the phenotypic selection of a transformed host cell. The regulatory elements for the expression in prokaryotes, e.g. *E. coli*, comprise the lac, trp promoter or T7 promoter, and those for the expression in eukaryotes comprise the AOX1 or

GAL1 promoter in yeast and those for the expression in animal cells comprise the CMV, SV40, RVS-40 promoter, CMV or SV40 enhancer. Further examples of suitable promoters are the metallothionein I and the polyhedrin promoters. Suitable vectors are e.g. expression vectors, based on T7, for the expression in bacteria (Rosenberg et al., Gene 56 (1987), 125), pMSXND for the expression in mammalian cells (Lee and Nathans, J. Biol. Chem. 263 (1988), 3521) and vectors derived from baculovirus for the expression in insect cells.

In a preferred embodiment, the vector containing the sequences coding for the RNA molecules according to the invention is a viral vector, e.g. a vaccinia virus or adenovirus, which is of use for a gene therapy. RNA viruses, above all retroviruses, are particularly preferred. Examples of suitable retroviruses are MoMuLV, HaMuSV, MuMTV, RSV or GaLV. For the purpose of gene therapy the RNA molecules according to the invention can be transported to the target cells in the form of colloidal dispersions as well. They comprise e.g. liposomes of lipoplexes (Mannino et al., Biotechniques 6 (1988), 682).

General methods known in the art can be used for constructing expression vectors which contain the sequences coding for the RNA molecules according to the invention and suitable control sequences. These methods comprise e.g. *in vitro* recombination techniques, synthetic methods and *in vivo* recombination methods, as described in Sambrook et al., for example.

The present invention also relates to host cells containing the above described vectors. These host cells comprise bacteria, yeast, insect and animal cells, preferably mammalian cells. Preferred mammalian cells are CHO, VERO,

BHK, HeLa, COS, MDCK, 293 and WI38 cells. Methods of transforming these host cells, of phenotypically selecting transformants and expressing the nucleic acid molecules according to the invention using the above described vectors are known in the art.

The present invention also relates to antibodies which detect specifically the RNA molecule according to the invention. The antibodies may be monoclonal, polyclonal or synthetic antibodies or fragments thereof, e.g. Fab, Fv or scFv fragments. In this case, a monoclonal antibody is preferably concerned. The antibodies according to the invention may be produced according to standard methods, the RNA molecule according to the invention or a fragment thereof serving as an immunogen. Monoclonal antibodies may be produced e.g. by the method described by Köhler and Milstein (Nature 256 (1975), 495) and Galfré (Meth. Enzymol. 73 (1981), 3), mouse myeloma cells being fused with immunized mammalian spleen cells. These antibodies may be used e.g. to inhibit the activity of the RNA molecules according to the invention, e.g. to influence the gene expression. The antibodies may also be used in diagnostic assays, for example, so as to prove whether dysregulation of the gene expression is accompanied e.g. by a loss or lack of responsible NINTROX-RNA. The antibodies may be present in immunoassays in liquid phase or be bound to a solid carrier. In this connection, the antibodies may be labeled in various ways. Suitable markers and labeling methods are known in the art. Examples of immunoassays are ELISA and RIA.

The invention also relates to antisense RNAs which bind specifically to an RNA molecule according to the invention and may be used *in vitro* or *in vivo* to reduce the expression of genes controlled directly by RNA, e.g. NINTROX-RNA. The

administration of the antisense RNA according to the invention to a target cell results in a reduced gene expression and is particularly useful for treating diseases which are characterized by an excessively great gene expression of the directly RNA-controlled gene (e.g. cancer diseases). In this connection, the antisense RNAs can be administered directly or as a DNA encoding the same, preferably inserted in a suitable vector. The suitable vectors comprise all of the vectors described above already in connection with the RNA molecules according to the invention.

The antisense RNAs according to the invention comprise an antisense sequence having at least 7 to 10 or more nucleotides which hybridize specifically with a sequence of the RNA molecule according to the invention, e.g. NINTROX-RNA. The antisense RNA according to the invention preferably has a length of about 10 to about 50 nucleotides or of about 14 to about 35 nucleotides. In further embodiments, the antisense RNAs according to the invention are RNAs shorter than about 100 nucleotides or shorter than about 200 nucleotides. In general, the antisense RNAs should be long enough to form a stable double helix but short enough (depending on the kind of supply) to be administered *in vivo*, if desired. In general, the antisense sequence is substantially complementary to the target sequence to ensure specific hybridization. In certain embodiments the antisense sequence is directly complementary to the target sequence. However, the antisense RNAs may also contain nucleotide substitutions, additions, deletions, transitions, transpositions or modifications as long as the specific bond to the relevant target sequence is maintained as a functional property of the antisense RNA. The antisense RNAs may also contain further sequences in addition to the

antisense sequences. The antisense RNAs (and the RNA molecules according to the invention) can be produced using any method suitable for the production of nucleic acids, e.g. by chemical synthesis *de novo* or by cloning. An antisense RNA may also be produced e.g. by inserting in a vector (e.g. a plasmid) a sequence of the target RNA or a fragment thereof in reverse orientation functionally linked with a promoter. Provided that the promoter and preferably termination and polyadenylation signals are positioned correctly, the strand of the inserted sequence is transcribed which corresponds to the non-coding strand acting as an antisense RNA.

The present invention also relates to ribozymes which cleave specifically the RNA molecules according to the invention and thus are also of use for inhibiting the gene expression. Useful ribozymes may comprise 5'-terminal and 3'-terminal sequences which are complementary to the target RNA, and they can be constructed by a person skilled in the art according to standard methods (see e.g. PCT publication WO 83/23572). The ribozymes according to the invention comprise e.g. ribozymes having the features of group I intron ribozymes (Cech, biotechnology 13 (1995), 323) and "hammerhead" ribozymes (Edgington, Biotechnology 10 (1992), 256).

In one embodiment, the ribozymes according to the invention *per se* are used as drugs. In another embodiment, gene therapy methods are employed for the expression of ribozymes in a target cell *ex vivo* or *in vivo*. The methods of administering the ribozymes or of expressing the ribozymes *in vivo* correspond to the methods described above in connection with the RNA molecules according to the invention.

The isolation and characterization of the human NINTROX gene and in particular the mouse homolog of the NINTROX gene allow to establish an animal model which permits to provide therapies and drugs for the above discussed diseases. Providing the sequence of the NINTROX gene enables both diagnosis (post-natally or pre-natally) and therapy of diseases in which the gene expression is characterized by the lack of NINTROX-RNA or an excess of NINTROX-RNA. However, the therapeutic or diagnostic application is not only limited to diseases, which are accompanied by a dysregulation of the expression of a gene controlled by NINTROX-RNA but the RNA molecules modified in accordance with the above described possibilities also offer the chance of using completely new therapeutic agents.

Therefore, the present invention also relates to drugs which contain the above described RNA molecules, vectors, antibodies, antisense RNAs or ribozymes. These drugs optionally contain additionally a pharmaceutically acceptable carrier. The person skilled in the art is familiar with suitable carriers and the formulation of such drugs. Suitable carriers include e.g. phosphate-buffered common salt solutions, water, emulsions, e.g. oil-in-water emulsions, wetting agents, sterile solutions, etc. The drugs can be administered orally or parenterally. The topical intra-arterial (e.g. directly to the tumor), intramuscular, subcutaneous, intramedullary, intrathecal, intraventricular, intravenous, intraperitoneal or intranasal administration belong to the methods for the parenteral administration. A suitable dose is determined by the attending physician and depends on various factors, e.g. on the age, sex, patient's weight, stage of a tumor, kind of administration, etc.

The drug according to the invention is used preferably for preventing or treating diseases which are correlated with a disturbed control of gene expression. The drug according to the invention is used particularly preferably for treating tumoral diseases or diseases of the CNS. In this connection, the drug may be used in gene therapy, the above described methods or vectors being usable for introducing the nucleic acids according to the invention. On the other hand, the RNA molecule according to the invention may be administered directly so as to restore normal expression of the gene in cells which no longer have functional copies of the RNA molecule.

The present invention also relates to a diagnostic composition which contains the RNA molecule according to the invention, to the DNA sequence coding for it or a fragment thereof, to the antibody according to the invention or a fragment thereof, or to the antisense RNA according to the invention or a fragment thereof, or to combinations thereof, optionally together with a suitable analytical reagent. By means of this diagnostic composition the detection may be made as to whether the RNA directly controlling the gene expression, e.g. NINTROX-RNA, is present or, as compared to a control, is available in excessively high or low concentration or with a deviating length. In this connection, the antibody or a fragment thereof is preferably used in the above described assays or the antisense RNA or a fragment thereof as a probe in hybridization experiments. For this purpose, the probe preferably has a length of at least 10, more preferably at least 15, bases. Suitable detection methods based on hybridization are known to the person skilled in the art. Suitable labeling for the probe are also known to the person skilled in the art and they comprise e.g. labeling using radioisotopes, bioluminescence,

chemiluminescence, fluorescence markers, metal chelates, enzymes, etc. This process may use methods known to the person skilled in the art as regards the preparation of whole RNA or poly(A)+RNA from biological samples, the separation of the RNAs on gels separating according to size, e.g. denaturing agarose gels, the production and labeling of the probe and the detection of the hybrids, e.g. via "Northern blot". In this connection, diseases are preferably diagnosed as described above in connection with the drugs according to the invention.

A diagnosis can also be made on a DNA level. In this connection, the intactness of the gene which codes for the RNA which is directly involved in the regulation of gene expression, e.g. NINTROX-RNA, is investigated by the above described nucleic acid molecules (e.g. as regards the availability, length or mutations). For this process it is possible to use methods with which the person skilled in the art is familiar as to the preparation of DNA from biological samples, the restriction digestion of the DNA, the separation of the restriction fragments on gels separating according to size, e.g. agarose gels, the production and labeling of the probe and the detection of hybridization, e.g. via "Southern blot". The above detection can also be carried out via PCR. In this connection, primers are used which flank the coding sequence. Here, amplification products of DNA from the tissue in question, which differ e.g. as regards the length or sequence from the amplification products of DNA from healthy tissue, are of diagnostic significance.

The subject matter of the present invention also relates to a non-human mammal whose NINTROX gene is modified, e.g. by

insertion of a heterologous sequence, in particular a selection marker sequence.

The expression "non-human mammal" comprises any mammal whose NINTROX gene may be modified. Examples of such mammals are mouse, rat, rabbit, horse, cow, sheep, goat, monkey, pig, dog and cat, with mouse being preferred.

The expression "NINTROX gene which is modified" signifies that in the NINTROX gene naturally occurring in a human mammal a deletion of about 1 to 2 kb is carried out by standard methods. If desired, a heterologous sequence, e.g. a construct for mediating antibiotic resistance (e.g. a "neo cassette") can be inserted in this deletion. This method is generally described in Schwartzberg et al., Proc. Natl. Acad. Sci. USA, Vol. 87, pp. 3210-3214, 1990, to which reference is made.

A further subject matter of the present invention relates to cells which are obtained from the above non-human mammal. These cells may be present in any form, e.g. in a primary or long-term culture.

A non-human mammal according to the invention can be provided by common methods. A method is favorable which comprises the steps of:

(a) preparation of a DNA fragment, in particular a vector, containing a modified NINTROX gene, the NINTROX gene having been modified by deletion of a homologous sequence and/or insertion of a heterologous sequence, in particular a selectable marker;

(b) preparation of embryonal stem cells from a non-human mammal (preferably mouse);

(c) transformation of the embryonal stem cells of step (b) with the DNA fragment from step (a), the NINTROX gene in the embryonal stem cells being modified by homologous recombination with the DNA fragment from (a);

(d) culturing the cells from step (c);

(e) selection of the cultured cells from step (d) for the absence of the homologous sequence and/or the presence of the heterologous sequence, in particular the selectable marker,

(f) production of chimeric non-human mammals from the cells from step (e) by injection of these cells in mammalian blastocysts (preferably mouse blastocysts), transfer of the blastocysts in pseudo-pregnant female mammals (preferably mouse) and analyses of the resulting offspring for a modification of the NINTROX gene.

The mechanism of the homologous recombination (cf. R.M. Torres, R. Kühn, Laboratory Protocols for Conditional Gene Targeting, Oxford University Press, 1997) is used in step (c) to transfect embryonal stem cells. The homologous recombination between the DNA sequences present in a chromosome and new, added cloned DNA sequences enables the insertion of a cloned gene in the genome of a living cell in place of the original gene. By this method it is possible to obtain via chimeras animals which are homozygous for the desired gene or the desired gene portion of the desired mutation when embryonal germ cells are used.

The expression "embryonal stem cells" comprises any embryonal stem cells of a non-human mammal which are suitable for the mutation of the NINTROX gene. The embryonal mouse stem cells, in particular cells E14/1 or 129/SV, are preferred.

The term "vector" comprises any vector which by recombination with the DNA of embryonal stem cells enables a modification of the NINTROX gene. The vector preferably has a marker with which it is possible to select for present stem cells in which the desired recombination was made. Such a marker is e.g. the loxP/tkneo cassette which by means of the Cre/loxP system can be removed from the genome again.

In addition, the person skilled in the art knows conditions and materials to carry out steps (a) to (f).

A non-human mammal is provided by the present invention whose NINTROX gene is modified. This modification can be an elimination of the gene expression-regulatory function. By means of such a mammal or cells therefrom the gene expression-controlling function of NINTROX can be investigated selectively. Furthermore, it is possible to find substances, drugs and therapy approaches by which a selective influence can be exerted on the controlling function of NINTROX. Therefore, the present invention furnishes a basis for influencing the most varying diseases. Such diseases are e.g. limitations of the CNS functions which reach as far as mental retardation or the induction of cancer resulting from mistakes made in the control of cell proliferation. Furthermore, it should be possible to investigate in more detail and characterize the part of the hippocampus.

The following clones were deposited with DSMZ, *Deutsche Sammlung von Mikroorganismen und Zellkulturen GmbH* [German-type collection of micro-organisms and cell cultures], Mascheroder Weg 1b, D-38124 Braunschweig, on May 4, 1998:

DSM 12153:	*E. coli* JFC-484, partial sequence of the human NINTROX-cDNA
DSM 12154:	*E. coli* JFC-622, partial sequence of the murine NINTROX-cDNA
DSM 12155:	*E. coli* JFC-8D3, sequence of the human genomic NINTROX-DNA
DSM 12156:	*E. coli* JFC-P1-165, sequence of the murine genomic NINTROX-DNA

The figures show:

Figure 1: human sequence of the NINTROX gene

Figure 2: murine sequence of the NINTROX gene

Figure 3: sequence comparison between human (top) and murine (bottom) sequences
Solid bars: sequence-conserved regions (b)

Figure 4: energy diagram of the sequences from figure 3

Figure 5: homology comparison of NINTROX from various species
Figure 5a: partial sequence from hamster
Figure 5b: partial sequence from kangaroo
Figure 5c: partial sequence from macaca
Figure 5d: partial sequence from orangutan
Figure 5e: partial sequence from rat

Figure 5f: partial sequence from chimpanzee

The following example explains the invention:

Example 1: Identification and Characterization of the NINTROX Gene

For the identification of transcribed sequences from the region Xq2-7.3 to Yqter, whole RNA was initially isolated from various pig tissues (kidney, heart, spleen, liver, brain, etc.) and transcribed by means of oligo-dT into first strand cDNA. These complex cDNA samples which represent all of the genes transcribed in the respective tissue were then labeled radioactively and hybridized with the Xq27.3-Xqter-specific cosmid library. The cosmid library was in this connection analyzed in the form of cosmid clones arranged systematically on nylon membranes. Then, the cosmid DNA was isolated by the cosmid clones which had positive hybridization signals with the complex cDNA samples, was digested using EcoRI, separated by gel electrophoresis and transferred to nylon membranes. The restriction fragments which then had a positive hybridization with the complex, radioactively labeled cDNA samples were subsequently isolated and labeled radioactively and used for screening a fetal human cDNA library. By this, positive cDNA clones could be isolated which represented the transcript of the NINTROX gene.

Claims

1. An RNA molecule which can bind to a ligand and comprises the following sequence regions:
   (a) a sequence region maintaining the three-dimensional structure of the RNA molecule; and
   (b) a sequence region for the specific binding of the ligand.

2. The RNA molecule according to claim 1, wherein sequence region (a) comprises the DNA sequence shown in fig. 3 without bars at the margin or a sequence which is related thereto and also permits the maintenance of the three-dimensional structure of the RNA molecule.

3. The RNA molecule according to claim 1 or 2, wherein sequence region (b) comprises the DNA sequence shown in fig. 3 with bars at the margin.

4. The RNA molecule according to any one of claims 1 to 3, wherein the ligand is a DNA molecule or a protein.

5. The RNA molecule according to any one of claims 1 to 4, which additionally contains a poly(A) sequence at the 3' end.

6. The RNA molecule according to any one of claims 1 to 5 for the control of gene expression.

7. The DNA sequence which codes for an RNA molecule according to any one of claims 1 to 6.

8. A gene which comprises the sequence shown in fig. 1 or 2.

9. A vector which comprises the DNA sequence according to claim 7 or the gene according to claim 8.

10. The vector according to claim 9, wherein the vector is a plasmid.

11. The vector according to claim 10, wherein the vector is a viral vector.

12. The vector according to claim 11, which is an RNA virus.

13. The vector according to claim 12, which is a retrovirus.

14. The host cell, containing the vector according to any one of claims 9 to 13.

15. The host cell according to claim 14, wherein the host cell is a mammalian cell.

16. An antibody or a fragment thereof, which bind specifically an RNA molecule according to any one of claims 1 to 6.

17. The antibody according to claim 16, wherein the antibody is a monoclonal antibody.

18. An antisense RNA which binds specifically to an RNA molecule according to any one of claims 1 to 6.

19. A ribozyme which cleaves specifically an RNA molecule according to any one of claims 1 to 6.

20. Use of the RNA molecule according to any one of claims 1 to 6, of the vector according to any one of claims 9 to 13, of the antibody or fragment thereof according to claim 16 or 17, of the antisense RNA according to claim 18 or of the ribozyme according to claim 19 for the production of a pharmaceutical preparation for preventing or treating diseases which are connected with a disturbed control of gene expression.

21. Use of the RNA molecule according to any one of claims 1 to 6, of the DNA sequence according to claim 7 or a fragment thereof, of the antibody or fragment thereof according to claim 16 or 17, or of the antisense RNA according to claim 18 or a fragment thereof for the diagnosis of diseases which are connected with a disturbed control of gene expression.

22. Use according to claim 20 or 21, wherein the disease is a tumoral disease or a disease of the central nervous system.

23. A non-human mammal whose NINTROX gene is modified by deletion of a homologous sequence and/or insertion of a heterologous sequence.

24. The non-human mammal according to claim 23, wherein the heterologous sequence is a selection marker sequence.

25. The non-human mammal according to claim 23 or 24, wherein the selection marker sequence conveys resistance to neomycin.

26. A process for the production of a non-human mammal according to any one of claims 23 to 25, characterized by the following steps:

(a) preparation of a DNA fragment, in particular a vector, containing a modified NINTROX gene, the NINTROX gene having been modified by deletion of a homologous sequence and/or insertion of a heterologous sequence, in particular a selectable marker;

(b) preparation of embryonal stem cells from a non-human mammal (preferably mouse);

(c) transformation of the embryonal stem cells from step (b) with the DNA fragment from step (a), the NINTROX gene in the embryonal stem cells being modified by homologous recombination with the DNA fragment from (a),

(d) culturing the cells from step (c),

(e) selection of the cultured cells from step (d) for the absence of the homologous sequence and/or the presence of the heterologous sequence, in particular the selectable marker,

(f) production of chimeric non-human mammals from the cells from step (e) by injection of these cells in mammalian blastocysts (preferably mouse blastocysts), transfer of the blastocysts into false-pregnant female mammals (preferably mouse) and analysis of the resulting offspring for a change of the NINTROX gene.

Abstract of the Disclosure

The invention relates to modularly constructed RNA molecules which can bind to a ligand and which are characterized by two sequence regions, namely a first sequence region which contributes to the maintenance of the three-dimensional structure of the RNA molecule, and a second sequence region which is responsible for the specific binding of the ligand. These RNA molecules, e.g. the NINTROX RNA, can be used for directly influencing the gene expression. The invention also relates to vectors containing the RNA molecules according to the invention as well as to medicaments and diagnostic compositions which contain said RNA molecules or vectors, to an antibody which specifically recognizes these RNA molecules or antisense RNA binding specifically to these RNA molecules, or to ribozymes cleaving these RNA molecules. In addition, the invention relates to non-human mammals whose NINTROX gene is modified by inserting a heterologous sequence and to cells obtained therefrom.

Human sequence of the non-coding RNA gene (including the putative promoter)

```
   1 CTTAGAGTTT CGTGGCTTCA GGGTGGGAGT AGTTGGAGCA TTGGGGATGT
  51 TTTTCTTACC GACAAGCACA GTCAGGTTGA AGACCTAACC AGGGCCAGAA
 101 GTAGCTTTGC ACTTTTCTAA ACTAGGCTCC TTCAACAAGG CTTGCTGCAG
 151 ATACTACTGA CCAGACAAGC TGTTGACCAG GCACCTCCCC TCCCGCCCAA
 201 ACCTTTCCCC CATGTGGTCG TTAGAGACAG AGCGACAGAG CAGTTGAGAG
 251 GACACTCCCG TTTTCGGTGC CATCAGTGCC CCGTCTACAG CTCCCCCAGC
 301 TCCCCCCACC TCCCCCACTC CCAACCACGT TGGGACAGGG AGGTGTGAGG
 351 CAGGAGAGAC AGTTGGATTC TTTAGAGAAG ATGGATATGA CCAGTGGCTA
 401 TGGCCTGTGC GATCCCACCC GTGGTGGCTC AAGTCTGGCC CCACACCAGC
 451 CCCAATCCAA AACTGGCAAG GACGCTTCAC AGGACAGGAA AGTGGCACCT
 501 GTCTGCTCCA GCTCTGGCAT GGCTAGGAGG GGGGAGTCCC TTGAACTACT
 551 GGGTGTAGAC TGGCCTGAAC CACAGGAGAG GATGGCCCAG GGTGAGGTGG
 601 CATGGTCCAT TCTCAAGGGA CGTCCTCCAA CGGGTGGCGC TAGAGGCCAT
 651 GGAGGCAGTA GGACAAGGTG CAGGCAGGCT GGCCTGGGGT CAGGCCGGGC
 701 AGAGCACAGC GGGGTGAGAG GGATTCCTAA TCACTCAGAG CAGTCTGTGA
 751 CTTAGTGGAC AGGGGAGGGG GCAAAGGGGG AGGAGAAGAA AATGTTCTTC
 801 CAGTTACTTT CCAATTCTCC TTTAGGGACA GCTTAGAATT ATTTGCACTA
 851 TTGAGTCTTC ATGTTCCCAC TTCAAAACAA ACAGATGCTC TGAGAGCAAA
 901 CTGGCTTGAA TTGGTGACAT TTAGTCCCTC AAGCCACCAG ATGTGACAGT
 951 GTTGAGAACT ACCTGGATTT GTATATATAC CTGCGCTTGT TTTAAAGTGG
1001 GCTCAGCACA TAGGGTTCCC ACGAAGCTCC GAAACTCTAA GTGTTTGCTG
1051 CAATTTTATA AGGACTTCCT GATTGGTTTC TCTTCTCCCC TTCCATTTCT
1101 GCCTTTTGTT CATTTCATCC TTTCACTTCT TTCCCTTCCT CCGTCCTCCT
1151 CCTTCCTAGT TCATCCCTTC TCTTCCAGGC AGCCGCGGTG CCCAACCACA
1201 CTTGTCGGCT CCAGTCCCCA GAACTCTGCC TGCCCTTTGT CCTCCTGCTG
1251 CCAGTACCAG CCCCACCCTG TTTTGAGCCC TGAGGAGGCC TTGGGCTCTG
1301 CTGAGTCCAA CCTGGCCTGT CTGTGAAGAG CAAGAGAGCA GCAAGGTCTT
1351 GCTCTCCTAG GTAGCCCCCT CTTCCCTGGT AAGAAAAAGC AAAAGGCATT
1401 TCCCACCCTG AACAACGAGC CTTTTCACCC TTCTACTCTA GAGAAGTGGA
1451 CTGGAGGAGC TGGGCCCGAT TTGGTAGTTG AGGAAAGCAC AGAGGCCTCC
1501 TGTGGCCTGC CAGTCATCGA GTGGCCCAAC AGGGGCTCCA TGCCAGCCGA
1551 CCTTGACCTC ACTCAGAAGT CCAGAGTCTA GCGTAGTGCA GCAGGGCAGT
1601 AGCGGTACCA ATGCAGAACT CCCAAGACCC GAGCTGGGAC CAGTACCTGG
1651 GTCCCCAGCC CTTCCTCTGC TCCCCCTTTT CCCTCGGAGT TCTTCTTGAA
```

Fig. 1

1701 TGGCAATGTT TTGCTTTTGC TCGATGCAGA CAGGGGGCCA GAACACCACA

1751 CATTTCACTG TCTGTCTGGT CCATAGCTGT GGTGTAGGGG CTTAGAGGCA

1801 TGGGCTTGCT GTGGGTTTTT AATTGATCAG TTTTCATGTG GGATCCCATC

1851 TTTTTAACCT CTGTTCAGGA AGTCCTTATC TAGCTGCATA TCTTCATCAT

1901 ATTGGTATAT CCTTTTCTGT GTTTACAGAG ATGTCTCTTA TATCTAAATC

1951 TGTCCAACTG AGAAGTACCT TATCAAAGTA GCAAATGAGA CAGCAGTCTT

2001 ATGCTTCCAG AAACACCCAC AGGCATGTCC CATGTGAGCT GCTGCCATGA

2051 ACTGTCAAGT GTGTGTTGTC TTGTGTATTT CAGTTATTGT CCCTGGCTTC

2101 CTTACTATGG TGTAATCATG AAGGAGTGAA ACATCATAGA AACTGTCTAG

2151 CACTTCCTTG CCAGTCTTTA GTGATCAGGA ACCATAGTTG ACAGTTCCAA

2201 TCAGTAGCTT AAGAAAAAAC CGTGTTTGTC TCTTCTGGAA TGGTTAGAAG

2251 TGAGGGAGTT TGCCCCGTTC TGTTTGTAGA GTCTCATAGT TGGACTTTCT

2301 AGCATATATG TGTCCATTTC CTTATGCTGT AAAAGCAAGT CCTGCAACCA

2351 AACTCCCATC AGCCCAATCC CTGATCCCTG ATCCCTTCCA CCTGCTCTGC

2401 TGATGACCCC CCCAGCTTCA CTTCTGACTC TTCCCCAGGA AGGGAAGGGG

2451 GGTCAGAAGA GAGGGTGAGT CCTCCAGAAC TCTTCCTCCA AGGACAGAAG

2501 GCTCCTGCCC CCATAGTGGC CTCGAACTCC TGGCACTACC AAAGGACACT

2551 TATCCACGAG AGCGCAGCAT CCGACCAGGT TGTCACTGAG AAGATGTTTA

2601 TTTTGGTCAG TTGGGTTTTT ATGTATTATA CTTAGTCAAA TGTAATGTGG

2651 CTTCTGGAAT CATTGTCCAG AGCTGCTTCC CCGTCACCTG GGCGTCATCT

2701 GGTCCTGGTA AGAGGAGTGC GTGGCCCACC AGGCCCCCCT GTCACCCATG

2751 ACAGTTCATT CAGGGCCGAT GGGGCAGTCG TGGTTGGGAA CACAGCATTT

2801 CAAGCGTCAC TTTATTTCAT TCGGGCCCCA CCTGCAGCTC CCTCAAAGAG

2851 GCAGTTGCCC AGCCTCTTTC CCTTCCAGTT TATTCCAGAG CTGCCAGTGG

2901 GGCCTGAGGC TCCTTAGGGT TTTCTCTCTA TTTCCCCCTT TCTTCCTCAT

2951 TCCCTCGTCT TTCCCAAAGG CATCACGAGT CAGTCGCCTT TCAGCAGGCA

3001 GCCTTGGCGG TTTATCGCCC TGGCAGGCAG GGGCCCTGCA GCTCTCATGC

3051 TGCCCCTGCC TTGGGGTCAG GTTGACAGGA GGTTGGAGGG AAAGCCTTAA

3101 GCTGCAGGAT TCTCACCAGC TGTGTCCGGC CCAGTTTTGG GGTCTGACCT

3151 CAATTTCAAT TTTGTCTGTA CTTGAACATT ATGAAGATGG GGGCCTCTTT

3201 CAGTGAATTT GTGAACAGCA GAATTGACCG ACAGCTTTCC AGTACCCATG

3251 GGGCTAGGTC ATTAAGGCCA CATCCACAGT CTCCCCCACC CTTGTTCCAG

3301 TTGTTAGTTA CTACCTCCTC TCCTGACAAT ACTGTATGTC GTCGAGCTCC

3351 CCCCAGGTCT ACCCCTCCCG GCCCTGCCTG CTGGTGGGCT TGTCATAGCC

3401 AGTGGGATTG CCGGTCTTGA CAGCTCAGTG AGCTGGAGAT ACTTGGTCAC

Fig. 1 (cont'd 1)

3451 AGCCAGGCGC TAGCACAGCT CCCTTCTGTT GATGCTGTAT TCCCATATCA

3501 AAAGGCACAG GGGACACCCA GAAACGCCAC ATCCCCCAAT CCATCAGTGC

3551 CAAACTAGCC AACGGCCCCA GCTTCTCAGC TCGCTGGATG GCGGAAGCTG

3601 CTACTCGTGA GCGCCAGTGC GGGTGCAGAC AATCTTCTGT TGGGTGGCAT

3651 CATTCCAGGC CCGAAGCATG AACAGTGCAC CTGGGACAGG GAGCAGCCCC

3701 AAATTGTCAC CTGCTTCTCT GCCCAGCTTT TCATTGCTGT GACAGTGATG

3751 GCGAAAGAGG GTAATAACCA GACACAAACT GCCAAGTTGG GTGGAGAAAG

3801 GAGTTTCTTT AGCTGACAGA ATCTCTGAAT TTTAAATCAC TTAGTAAGCG

3851 GCTCAAGCCC AGGAGGGAGC AGAGGGATAC GAGCGGAGTC CCCTGCGCGG

3901 GACCATCTGG AATTGGTTTA GCCCAAGTGG AGCCTGACAG CCAGAACTCT

3951 GTGTCCCCCG TCTAACCACA GCTCCTTTTC CAGAGCATTC CAGTCAGGCT

4001 CTCTGGGCTG ACTGGGCCAG GGGAGGTTAC AGGTACCAGT TCTTTTAGAA

4051 GATCTTTGGG CATATACATT TTTAGCCTGT GTCATTGCCC CAAATGGATT

4101 CCTGTTTCAA GTTCACACCT GCAGATTCTA GGACCTGTGT CCTAGACTTC

4151 AGGGAGTCAG CTGTTTCTAG AGTTCCTACC ATGGAGTGGG TCTGGAGGAC

4201 CTGCCCGGTG GGGGGGCAGA GCCCTGCTCC CTCCGGGTCT TCCTACTCTT

4251 CTCTCTGCTC TGACGGGATT TGTTGATTCT CTCCATTTTG GTGTCTTTCT

4301 CTTTTAGATA TTGTATCAAT CTTTAGAAAA GGCATAGTCT ACTTGTTATA

4351 AATCGTTAGG ATACTGCCTC CCCCAGGGTC TAAAATTACA TATTAGAGGG

4401 GAAAAGCTGA ACACTGAAGT CAGTTCTCAA CAATTTAGAA GGAAAACCTA

4451 GAAAACATTT GGCAGAAAAT TACATTTCGA TGTTTTTGAA TGAATACAAG

4501 CAAGCTTTTA CAACAGTGCT GATCTAAAAA TACTTAGCAC TTGGCCTGAG

4551 ATGCCTGGTG AGCATTACAG GCAAGGGGAA TCTGGAGGTA GCCGACCTGA

4601 GGACATGGCT TCTGAACCTG TCTTTTGGGA GTGGTATGGA AGGTGGAGCG

4651 TTCACCAGTG ACCTGGAAGG CCCAGCACCA CCCTCCTTCC CACTCTTCTC

4701 ATCTTGACAG AGCCTGCCCC AGCGCTGACG TGTCAGGAAA ACACCCAGGG

4751 AACTAGGAAG GCACTTCTGC CTGAGGGGCA GCCTGCCTTG CCCACTCCTG

4801 CTCTGCTCGC CTCGGATCAG CTGAGCCTTC TGAGCTGGCC TCTCACTGCC

4851 TCCCCAAGGC CCCCTGCCTG CCCTGTCAGG AGGCAGAAGG AAGCAGGTGT

4901 GAGGGCAGTG CAAGGAGGGA GCACAACCCC CAGCTCCCGC TCCGGGCTCC

4951 GACTTGTGCA CAGGCAGAGC CCAGACCCTG GAGGAAATCC TACCTTTGAA

5001 TTCAAGAACA TTTGGGGAAT TTGGAAATCT CTTTGCCCCC AAACCCCCAT

5051 TCTGTCCTAC CTTTAATCAG GTCCTGCTCA GCAGTGAGAG CAGATGAGGT

5101 GAAAAGGCCA AGAGGTTTGG CTCCTGCCCA CTGATAGCCC CTCTCCCCGC

5151 AGTGTTTGTG TGTCAAGTGG CAAAGCTGTT CTTCCTGGTG ACCCTGATTA

5201 TATCCAGTAA CACATAGACT GTGCGCATAG GCCTGCTTTG TCTCCTCTAT

Fig. 1 (cont'd 2)

5251 CCTGGGCTTT TGTTTTGCTT TTTAGTTTTG CTTTTAGTTT TTCTGTCCCT

5301 TTTATTTAAC GCACCGACTA GACACACAAA GCAGTTGAAT TTTTATATAT

5351 ATATCTGTAT ATTGCACAAT TATAAACTCA TTTTGCTTGT GGCTCCACAC

5401 ACACAAAAAA AGACCTGTTA AAATTATACC TGTTGCTTAA TTACAATATT

5451 TCTGATAACC ATAGCATAGG ACAAGGGAAA ATAAAAAAAG AAAAAAAAGA

5501 AAAAAAAACG ACAAATCTGT CTGCTGGTCA CTTCTTCTGT CCAAGCAGAT

5551 TCGTGGTCTT TTCCTCGCTT CTTTCAAGGG CTTTCCTGTG CCAGGTGAAG

5601 GAGGCTCCAG GCAGCACCCA GGTTTTGCAC TCTTGTTTCT CCCGTGCTTG

5651 TGAAAGAGGT CCCAAGGTTC TGGGTGCAGG AGCGCTCCCT TGACCTGCTG

5701 AAGTCCGGAA CGTAGTCGGC ACAGCCTGGT CGCCTTCCAC CTCTGGGAGC

5751 TGGAGTCCAC TGGGGTGGCC TGACTCCCCC AGTCCCCTTC CCGTGACCTG

5801 GTCAGGGTGA GCCCATGTGG AGTCAGCCTC GCAGGCCTCC CTGCCAGTAG

5851 GGTCCGAGTG TGTTTCATCC TTCCCACTCT GTCGAGCCTG GGGGCTGGAG

5901 CGGAGACGGG AGGCCTGGCC TGTCTCGGAA CCTGTGAGCT GCACCAGGTA

5951 GAACGCCAGG GACCCCAGAA TCATGTGCGT CAGTCCAAGG GGTCCCCTCC

6001 AGGAGTAGTG AAGACTCCAG AAATGTCCCT TTCTTCTCCC CCATCCTACG

6051 AGTAATTGCA TTTGCTTTTG TAATTCTTAA TGAGCAATAT CTGCTAGAGA

6101 GTTTAGCTGT AACAGTTCTT TTTGATCATC TTTTTTTAAT AATTAGAAAC

6151 ACCAAAAAAA TCCAGAAACT TGTTCTTCCA AAGCAGAGAG CATTATAATC

6201 ACCAGGGCCA AAAGCTTCCC TCCCTGCTGT CATTGCTTCT TCTGAGGCCT

6251 GAATCCAAAA GAAAAACAGC CATAGGCCCT TTCAGTGGCC GGGCTACCCG

6301 TGAGCCCTTC GGAGGACCAG GGCTGGGGCA GCCTCTGGGC CCACATCCGG

6351 GGCCAGCTCC GGCGTGTGTT CAGTGTTAGC AGTGGGTCAT GATGCTCTTT

6401 CCCACCCAGC CTGGGATAGG GGCAGAGGAG GCGAGGAGGC CGTTGCCGCT

6451 GATGTTTGGC CGTGAACAGG TGGGTGTCTG CGTGCGTCCA CGTGCGTGTT

6501 TTCTGACTGA CATGAAATCG ACGCCCGAGT TAGCCTCACC CGGTGACCTC

6551 TAGCCCTGCC CGGATGGAGC GGGGCCCACC CGGTTCAGTG TTTCTGGGGA

6601 GCTGGACAGT GGAGTGCAAA AGGCTTGCAG AACTTGAAGC CTGCTCCTTC

6651 CCTTGCTACC ACGGCCTCCT TTCCGTTTGA TTTGTCACTG CTTCAATCAA

6701 TAACAGCCGC TCCAGAGTCA GTAGTCAATG AATATATGAC CAAATATCAC

6751 CAGGACTGTT ACTCAATGTG TGCCGAGCCC TTGCCCATGC TGGGCTCCCG

6801 TGTATCTGGA CACTGTAACG TGTGCTGTGT TTGCTCCCCT TCCCCTTCCT

6851 TCTTTGCCCT TTACTTGTCT TTCTGGGGTT TTTCTGTTTG GGTTTGGTTT

6901 GGTTTTTATT TCTCCTTTTG TGTTCCAAAC ATGAGGTTCT CTCTACTGGT

6951 CCTCTTAACT GTGGTGTTGA GGCTTATATT TGTGTAATTT TTGGTGGGTG

Fig. 1 (cont'd 3)

```
7001  AAAGGAATTT TGCTAAGTAA ATCTCTTCTG TGTTTGAACT GAAGTCTGTA
7051  TTGTAACTAT GTTTAAAGTA ATTGTTCCAG AGACAAATAT TTCTAGACAC
7101  TTTTTCTTTA CAAACAAAAG CATTCGGAGG GAGGGGGATG GTGACTGAGA
7151  TGAGAGGGGA GAGCTGAACA GATGACCCCT GCCCAGATCA GCCAGAAGCC
7201  ACCCAAAGCA GTGGAGCCCA GGAGTCCCAC TCCAAGCCAG CAAGCCGAAT
7251  AGCTGATGTG TTGCCACTTT CCAAGTCACT GCAAAACCAG GTTTTGTTCC
7301  GCCCAGTGGA TTCTTGTTTT GCTTCCCCTC CCCCCGAGAT TATTACCACC
7351  ATCCCGTGCT TTTAAGGAAA GGCAAGATTG ATGTTTCCTT GAGGGGAGCC
7401  AGGAGGGGAT GTGTGTGTGC AGAGCTGAAG AGCTGGGGAG AATGGGGCTG
7451  GGCCCACCCA AGCAGGAGGC TGGGACGCTC TGCTGTGGGC ACAGGTCAGG
7501  CTAATGTTGG CAGATGCAGC TCTTCCTGGA CAGGCCAGGT GGTGGGCATT
7551  CTCTCTCCAA GGTGTGCCCC GTGGGCATTA CTGTTTAAGA CACTTCCGTC
7601  ACATCCCACC CCATCCTCCA GGGCTCAACA CTGTGACATC TCTATTCCCC
7651  ACCCTCCCCT TCCCAGGGCA ATAAAATGAC CATGGAGGGG GCTTGCACTC
7701  TCTTGGCTGT CACCCGATCG CCAGCAAAAC TTAGATGTGA GAAAACCCCT
7751  TCCCATTCCA TGGCGAAAAC ATCTCCTTAG AAAAGCCATT ACCCTCATTA
7801  GGCATGGTTT TGGGCTCCCA AAACACCTGA CAGCCCCTCC CTCCTCTGAG
7851  AGGCGGAGAG TGCTGACTGT AGTGACCATT GCATGCCGGG TGCAGCATCT
7901  GGAAGAGCTA GGCAGGGTGT CTGCCCCCTC CTGAGTTGAA GTCATGCTCC
7951  CCTGTGCCAG CCCAGAGGCC GAGAGCTATG GACAGCATTG CCAGTAACAC
8001  AGGCCACCCT GTGCAGAAGG GAGCTGGCTC CAGCCTGGAA ACCTGTCTGA
8051  GGTTGGGAGA GGTGCACTTG GGGCACAGGG AGAGGCCGGG ACACACTTAG
8101  CTGGAGATGT CTCTAAAAGC CCTGTATCGT ATTCACCTTC AGTTTTTGTG
8151  TTTTGGGACA ATTACTTTAG AAAATAAGTA GGTCGTTTTA AAAACAAAAA
8201  TTATTGATTG CTTTTTTGTA GTGTTCAGAA AAAAGGTTCT TTGTGTATAG
8251  CCAAATGACT GAAAGCACTG ATATATTTAA AAACAAAAGG CAATTTATTA
8301  AGGAAATTTG TACCATTTCA GTAAACCTGT CTGAATGTAC CTGTATACGT
8351  TTCAAAAACA CCCCCCCCCC ACTGAATCCC TGTAACCTAT TTATTATATA
8401  AAGAGTTTGC CTTATAAATT TA
```

Fig. 1 (cont'd 4)

Murine sequence of the non-coding RNA gene (including the putative promoter)

```
   1  CTTAGAGTTT CGTGGCTTCG GGGTGGGAGT AGTTGGAGCA TTGGGATGTT
  51  TTTCTTACCG ACAAGCACAG TCAGGTTGAA GACCTAACCA GGGCCAGAAG
 101  TAGCTTTGCA CTTTTCTAAA CTAGGCTCCT TCAACAAGGC TTGCTGCAGA
 151  TACTACTGAC CAGACAAGCT GTTGACCAGG CACTCCCCCC AACAATATCC
 201  TCCCTCTTCC CCCCCCCCAC CCCCGCCCCG TGTGCTCGTT AGGGCAATTG
 251  AAAGGACACT CCCATTTTTG GTGCCATTGA TGCCCTGTCC ATAATAGCTT
 301  CCCTGACTTT TACACCACCC CAACTCCCAA TCTGAAGGAC TGGGAGGTGT
 351  GATGCAGGAG AAACTATGGG ACTCTTGGGA GAAGACTATG GAGTTGGCCA
 401  GTGATTAAGG CCCACTAATT CCAACTGTGG TAGCACAGAT CTGGCTCCAC
 451  ATCAACCCAA TCCAAAACTG ACAAGGATAT TTTGCAAAAA AAGAAAGTGG
 501  CACCTGTCTG ATCCAGCTCT GACATGGCTA GAGGTGAGTC CTAAACTGAT
 551  GGCTTATAAA CTAGCCTGAG CCACAGAAGA GTATGGCCCA GAGTGAAGTG
 601  TCATCATCTG TTCACAAGGC ATGCTCCCCT AGAAGATAAT GCTAAAGAGG
 651  TGCCATGGAG GCAGCAGGAC AAAGTACAGG CAGGCTAGGT GGAGTCAAGC
 701  CAGGCCTAGT GCCACAGAAC AAGAGAGCAG TCTGACTAGT AATTAAGAGG
 751  GAAGAAAGGA AAATATTCTT CCAATTACTT TCCAGTTCTC CTTTAGGGAC
 801  AGCTTAGAAT TATTTGCACT ATTGAGTCTT CATGTTCCCA CTTCAAAACA
 851  AACAGATGCT CTGAAAGCAA ACTGGCTTGA AATGGTGACA CTGTCCCACA
 901  AGCCACCAGA CATGGCAGTG TTCAGAACTA CCTGTATCTG TATATACCTG
 951  CGCTTGTTTT AAAGTGGGCT CAGCACATAG GATTCCCAAG AAGCTCCGAA
1001  ACTCTAAGTG TTTGCTGCAA TTTTATAAGG ACTTCCTGAT TGCTTTCTCT
1051  CTCGTCCTTC CATTTCTTCC TTCCTTCCAT TTCATGCTTT CATTTCTTCC
1101  CCTAGCTTCT AGTTGTTTCT TCTGTTCCAG GCAGCTGCAG TGCTGAACCA
1151  CATGGTTACC TAACAGCAGT CAGCTGCAGC CCTAGGATTC TTCCTGCCCT
1201  TTAACTTCCC ATTGCCAGTG CCAGGTATCA TATTTAACCT TGAGCAAGAG
1251  CTGGGCTCTT TTGAGCCCTC CCTAACCTCT GTGAAGAAGA ACAAGAAGGT
1301  AGGAAGCTCT TGCTCTTGCT AAGAAAAATG TCAAAAGGCT TTCAGACCTT
1351  AAACAATGAG CCTTTTCACC TTTTACTCTA GAAAAGTGGA CTAGAAAATC
1401  TGGGTCACAT TGGGTAGCTG AAGGAGATAC AGAGGCCCCT ATGGCCTGCC
1451  AGAGTCGTTG CATGGCCCAA CAGGGGCTCC ATGCCCACTA CCCTTGACCC
1501  TACTCAGAAA TCTAATGTCA TACTTAGTGT GGGCAGGGGA CCTGTCAGGA
1551  CAGATGCAGA CCTAAGCAGG GAGTGACACC AGGGCCCTTG GCCCTTCTTC
1601  TGACAAACAT ACACATCCCA AGTCTTTTTC TAGTGGAATT CTTAACCTCT
1651  TGCTCACTGG GGACTGGGAA GCATCAGCAC ATCCCATATT TCAAACTCTG
```

Fig. 2

1701 CTCCATAAGT ACAGTGGTGA ATTTTATAGA CTTGACTTTG CTGTGGGGTT

1751 TTAATTGGTC AGTTTTAATT TGGGATCCCA AAGTTTTAAC CTCCATTCAG

1801 GAAGTCCTTA TCTAGCTGCA TATCTTCATC ATATTGGTAT ATCCTTTTCT

1851 GTGTTTACAG AGATGTCTCA TATCTATCGA AATCTGTCTG AGAAGTACCT

1901 TATCAAAGTA GCAAATGAGA CAGCAGTCTT ATGCTTCCAG AAACACCCAC

1951 AGGCACGTCC CATGTGAGCT GCTGCCATGA ACTGTCGAGT GTGTATTGTC

2001 TTGTGTATTT TCGTTAACGT TCCCCAGCTT CCTTCCTGCG GTGTAATCAT

2051 GGAAGAGTGA AACATCATAG AAATCGTCTA GCACTTCCTG GCCAGTCCTT

2101 AGTGATCAGG AACCGTAGTT GACAGTTCCA ATTGATAGCT TAAGATAAAA

2151 CCATGTTTGT CTCTTATGGA ATGGTTAGAA CTAAGTGAGA GATCTTGCCC

2201 CATTCTGTTT GCCGAATCAT AGTTGGACTT TTAGTGTATT TGTATCCATT

2251 TCCTTGTGCT ATAAAAGCAA ACCCTGCAAC CAGCTTTCTG TCAGGCAGTC

2301 CTTTTGCCTG CTCTGCTTTT GATCCTCTTA GTCTTGCTTC TGGTTCCTCC

2351 CTGGAGAGGG AGGAGGGGTC AGAAGAGGAA TTCTGGAGGA TCCAGGATAT

2401 GTCCTTCTGA ACTCCTGCTT CTTCCAGTGA CAAAAGGCCC CTACTGCCCC

2451 ACCCCAACCT GCCCCATGCA CTCCTCTAGG ACACCTTTCC ATACTTTTCA

2501 CAACACCTAG CCAGGTTGAC ACCAAGTTGT TTATTGTGGT CTGCTTGGAA

2551 TTTTACCTGT TAGGCTTACT TAGTCCAATC AAATGGACTC CAAGTTGGGT

2601 ATCCCTCATC TTTGGAAGAC AACCTAGGCT GATTAGATAT TTACTTTTGG

2651 GATTGCAGCA CTTTGGGTGC CGTTTTTCTT TTACTTGGGT TTTATCTGCA

2701 GCTCCCTCAC CACCACCACC ACCCCCCACT TACCTGTATG TAGAACTGAT

2751 TTCAAAACTG CAGGTGGTGG TAACTGCAGC TTCTTAGGGT TTTCTTCACT

2801 TCTTGCTTCT TTCCCCATTC CCTCATCCAC AAATAAGGGC ATCACAAGTC

2851 AGTCTCCTTT AAGCAGGCAG CTTTGGTGGG GTTTTTCCCC TGGAAGCCAG

2901 GGACCCTGTC AGGCTGCCTC TGCCTTGTGG TCAGGTTGAC AGGAGGTTGG

2951 AGGGAAAAGC CTTAAGTCAT GGGATTCTCA CCAGCTGTGT CTGGCTCAGA

3001 CCTGGAATGT GACCTTTATT TTGTTGTATT TGAACATTGT AAAGTGTGGG

3051 TGGTACCTTA AACTGAATAT GTGAAGAATC CAGAAACTGA CCAACAGCTT

3101 TCAGATACCT GGGGCTAGGT CACTAAGGTC ACATCCAGTC TTCCCTACCC

3151 TGTTCTAGTT GTTAGCTACT ACCTCTCCCA GATAGATTGC TGTATATCCT

3201 CCAACTATGA TCATCCTGGC CCAAGCTTGC CTGTTCTTGA GTCTGTCTTA

3251 ACCAGTGGAA CTGCTGCCCT TGGTGTGCAG TGAGTTGAGG ACTCTTGGTC

3301 ACAGCCAGGC TCTAGTAGTA CAGCTCCTTT CTGCTGGTGC TGTATTTCCA

3351 TATCAAAAGG CACAGGGGAG ATCTAGAAAT GCCATCTCCC CCAGTCCATC

3401 AGTGCCAAAC AAGCCCATGA TCCCAGCATG GGTACAGACA ACTCTGTTCA

Fig. 2 (cont'd 1)

3451 GTGCTATCAC AACAGACTAG AGGCCATGAA CATTGGACGT GGGAACCAGA

3501 GCAACCCGAA TTGCTGCTGC TTTATTCAGC TTTCCGTTGC TCTGACAATG

3551 ATAAAACAAG GCAGTAACTT AAAACAGACT GCCAGGTTTG GCAGAGAAAG

3601 GAAATTCCTT AGCTGACAGC ACCTCTGGAT TTTAAATAGG TTGTAATAAG

3651 TGGCTCAAAC CCATCCAGGA AAAAGCAAAA GGGTTAGAAC TGACCAGATG

3701 AGACCAGCCT GATTTCATGC AGCCCAAATG GAGTCCAGCT GTCTGAACTC

3751 TGCAGCACTT CTCTACTACA GTCTCCTAGA GCATTCCAGC CAGGCTCTTC

3801 AGGCTGAGGA GACATCACAG GTGCCAGTTC TTCAAGAAGA CTTTTGTGCA

3851 TCAGTTCATA GCCTATATCT TTGCCCAAGA TTGTAGATTC AGGTTAACAC

3901 TACAGATTCT AGGGCAGATG ACTGAGACTC AGAAAAAAAG CCCCTGTGGA

3951 CTGTGGTATA GCGAAGTACA AAAACTGAAG GGGGCTAGGG CAGATGCCGC

4001 ATGCCTCATG CCAGAGCCAA GCCCTCTGCT CCATCCACAT CCTTTTCTGG

4051 CTCCTTCTTC CTGCTCTCTG CTTCAGTGAA CCAGCCCCAC TCTGAAGAGA

4101 TTTGTTGATT CTCTCCATTT TTATGTCTTT CTCTTTTAGG TACTATATAG

4151 AAAAGGCTTA GTCTAATTGT TATAAATTGC TAGAATACTG CCTCCCCCAG

4201 GGTCTAAAAA TATATGCTAA AGGGGAAAAC TTGAACACTG AAACCAGTTC

4251 TGAACAATTT AGAAGGAAAA CCTTGAAAAC ATTTAACAAA AAATTATATT

4301 TTAATGTTTA TGAATAAGAG GAGGCTTTTG AAAAAATGTT GATCTATAAA

4351 TACTTACTTT AGGCCTGAGG TGTCTAATGA GTGAACTGAG CAATGGGAAC

4401 TCAAGGCTGA AGCCTCCTGC ATCAGAGGAG GTAGAACCAG GAGCCTCTTG

4451 AGATTTGAGG TGTTTTAGCA TTGGAAAGCC ACTCTTTGGG TAGCTGGCCC

4501 CAGAAACTAC TTCTGACCTT GTCATTTGGA ATGGAGGTTA GTGGTCTGCC

4551 AGATGCCAAA GCTGCATGAG ACCAGCTCTT GGTTTATCAA TTTGAACACT

4601 CAGTAACCTA GAAGGCCCAG CACAAAGTGT CTGCTCTCTT CTTAACTGAG

4651 CCTGCCCCAG CACTACTGCA CAAATTAGGG AGGGTCTACT TCCTACAGAG

4701 CATCCCTCCC TGGGCCCCCT CCCATCCTTT GTACTCTACC TACCTGACCT

4751 TCAGGATCTT GGCACATACG AAATGGCTGT GTAGCAAGCA CTTTGGCATG

4801 CCCTCCTAAA CTTACCCCAG AGCCTCTCCC TGCCTCCTTA AGCCAGTCTG

4851 CCTGTCTTCT GGGGAGGTGT TAGAGCCCAT AGAATGGAGA GGAGAAAGAA

4901 AAGAGGAAGA GGCAGGCAGG TAGTAAAAAG GCTCTGGGAG GAAAGACAGC

4951 CTCCTAGGCT TTGCACAAGC AGGACTCAGC CCCTTGTGGG AACTAAGTGC

5001 CATCTTGGAG TTTAAGAACA TTTGGACAAG TTGCAAATGA CCTTTGCTCC

5051 TTGCTCCTCT CACCTTTTAT GGGGCCCTGC TTAGCACTGA AAGCAAATGC

5101 GCTGAAAAGG CAAAGAGGTT TGGCTCCTGC CCACTGATAG TCCTTTCCCT

5151 GCAGTGTTTG TGTGTCAAGT GGCAAAGCTG TTCTTCCTGG TGACTCTGAT

5201 TAGATCCAGT AACTTAAGAG ATTTGTATGC ATAGGTCTGC TTTGACTCTT

Fig. 2 (cont'd 2)

5251 CTATTCTGGG CTTTTGATTT GTTTTTCAGT TTTGCTTTTA GTTTTCCTAT

5301 TTTTATTTTA TGCACCAACT AGACACACAA AGCAGTTGAA TTTATATATA

5351 TATATATATA TATATATCTG TATATTTCAC AATTATAAAC TCATTTTGCT

5401 TGTGACGCCA CACACACACA AAAAGAAAAA CCTTTTAAAA TTATACCTGT

5451 TGCTTAATTA CAATATTTCT GATAACCATA GAGTAGGACA AGGGAAAAAA

5501 TTTAAAAAAA AAAAAAAAAA AAGAAAAAAC ACATCTGTCT GCTGGTCACT

5551 TCTTCAATCC AAGCAGATCT GTGATCTTTC CTCGCGTCTT TCAAAGACTT

5601 CCCTGTGCTA AGTGAAGGAA GCTCCAGGCT GCACCCAGGT TTTGTGCTTT

5651 GTTTCTCCTC TGTTGTGAAA GGGGCCCCAA GATTCTGGGT ACAGGACAGT

5701 TCATTTCAGC ATGGGGTCAG GAGACAAGAG CACTCCCTTT ACATGCTGAC

5751 GTACAGAACT TAGTGGGAAT AGCCTAGTCC CCACCTCTAG GGATGGGGAG

5801 CTAGCATGCA TGGGGGTGAC CCAACTCCCT CCACCTTTCC CTGGCCAGGA

5851 AGAGCCTGTG TACAGTAAGT CTGACAAGCT TTCCCCAGTT AGCAGGGCTC

5901 AGAGCATTTA AAAACCCTCC AAACTTTGCT GAGTCTAGGG ACTAGAGAGA

5951 AGATAGAAGA TTTGGTCTAT CTCCAAGGTG TGTAAGCTGT ACCAGGTAGA

6001 ATGCCAGGGA CCCCAGAACC ACATCCAACA GCCCAATGGG TCTCCTCCAG

6051 AAAGTAGTGA AGACTCCAGA AACATCCCTT TCTCTTCTCC CTGCTCCCAT

6101 GAGTAACTGC ATTTGCTTTT GTAATCCTTA ATGAGCATTA TCTGCTAAAA

6151 AAAAAAAATT AGCTGTAACA GTTCTTTTTG CAAAAGGATC ATTCTTAAAT

6201 AATTAAAAAC ACCCCCCCCC CAAAAAAAAG TCCAGAACCT TGTTCTTCCA

6251 AAGCAGAGAG CATTATAATC AGGGCCAAAA TCTGTCCCAC ACCTCTACCC

6301 CATCTCCTCA TGATTGCTGC TTCTAAGGCC AGAATACAGC AAAGATATTT

6351 GTAGGCCCTT TGGGTGACTG GGCTACCCTT GGAGCTCTTG GAAGATGGGC

6401 TGGGGAAGCC TCTGAGACCC TATCCTAGGG CCTTGCTCTA GGGAGTAATC

6451 AGTATTAGTA GAGTGTCACA ACATTATTCC CCAGCCGGCA TGAGATGGGG

6501 GCAGAAGAAG CCAAAGGGTT GTCTCCACTG CTACTTACTT GGCCACTGAC

6551 AGGTAGGTGA CCATGTATGT CCATATGCAT GTTTTATGGC TGATGTGAGA

6601 TCAGCACCCA AGTTAGCTTC ACCTGGTGAC CTCTAACCCT GCCTGGATGG

6651 AGCAGGCCAC CTGGTTCAAT GTTTCTGGGC AGCTGGACAA TGGAGTGCAA

6701 AAGGCTTACA GAACTTGAAG CCTTTTCCTT ACTTTGCTAG CACGGCCTCC

6751 TTTTCCATTT GATTTGTCAC TGCTTCAGTC AATAACAGCC GCTCCAGAGT

6801 CAGTAGTTGA TGAATATATG ACCAAATATC ACCAGGACTG TTACTCAACG

6851 TGTGCCGAGC CCTTTCCTTG TGCTGGGCTC CCTGTGTACC TGGACACTGT

6901 AATGTGTGCT GTGTTTGCTC TCCTTCCTCT TCCTTCCTTG CCCTTTCCTT

6951 GTCTTTCTGG GGTTTTTCTG TTGGGTTTGG TTTGGTTTTA TTTTTCCTTT

Fig. 2 (cont'd 3)

```
7001  TGTGTTCCAA ACATGAGGTT TTCTCTACTG GTCCTCTTTA ACTGTGGTGT
7051  TGAGGCTTCT ATTTGTGTAA TTTTTGGTGG GTGAAAGGAA CTTTGCTAAG
7101  TAAATCTCTT CTGTGTTTGA AATGAAGTCT GTATTGTAAC TATGTTTAAA
7151  GTAATTGTTC CAGAGACAAA TGCTTCTAGG TACATTTTCA TTACAAACAA
7201  AGCATTTGAA GGGAGGGAAG TGGTGAATAA GACAAGAGGG GCAATCTGAA
7251  TTGATCCCTG CCCAGATCAG CCAGAAGCTA CCAAAAGTTA AGCACTGGTT
7301  TTCCATTCCA AGTCAAGAGA CTGAAGCTGA TGTTTTGCCA TTTTCAAAGT
7351  CAAAGCAAAA CCAGCTTTTC CACCCAATGG ATTCTTTGCT TCTCCTTCCC
7401  AGATTATTAC TACTGCTGTA ATAATCTAGG AGTGCCAGGA GGGAAAGGAG
7451  TATTAACACA GAGCTGTGCT CACTGAGTAT GGAAAGGCTT GGTCTGAGTT
7501  TTCAGGAGGA TGACCCACTG TGGACATGGG GAGAAGACAG AAGATAAATT
7551  AGCCGCTCCC TGCCTAAGAT ACCTCTTAAT AGATAAGTCA AGGCCATGGA
7601  CATTATTGTC TACAAGGCAT GTTTCAAAGA CATGACCAGT CAGGACACTT
7651  CTGTCATACT CCATGTTGCC CCCTAGTACA CAGTACTAAT CTGATATCTC
7701  TGTTCCCGCC ATGCCTGGGG GATAAAATGA TAGCAGAGAC TCCTTTCCTT
7751  CAATGTGATC TAATTCCCAA CAAAATCTGG GCCTGAGATA CCACCTGTTT
7801  CTATGGCAAA CATCCTCAGT AAAGTGTTAT TCTCATTGCA GATTGTTCCA
7851  GCCTAATGTA AGAGGAACAG AGCAGTGTTC CCTTGGAGCC TCATGTGGAC
7901  AGTTCTACCT GTAGTGACCA GTTGGCTATA GTAGTTATTA GCTGGAACAA
7951  CCAGACAGGG TACATGCCCC CTCCAAAATC CATGTTGTAC TCCCCTCTGC
8001  CAGCCAGGGG GGGTGAGATC TGTAGAATAG TGCAGCCAGT GACAAGCCAC
8051  CTTGTGTTTG TCACCAGCTC AAAAACTCAT CTAAGGTTGG GAGCAGGCAG
8101  ACAAGGCAGA GAGAAAGATC CAGGACAGAC CTAGCTGGGC TGGAGGGGTC
8151  TTGAAAAGCC CTCTGTCGTA TTCACCTTCA GTTTTTGTGC TTTGGGACAA
8201  TTACTTTAGA AAATAAGTAG GTCGTTTTAA AAACAAAATA TTGATTGCTT
8251  TTTTGTAGTG TTCAAAACAA AAGGTTCTTT GTGTATAGCC AAATGACTGA
8301  AAGCACTGAT ATATTTAAAA ACAAAAGGCA ATTTATTAAG GAAATTTGTA
8351  CCATTTCAGT AAACCTGTCT GAATGTACCT GTATACGTTT CAAAAACACA
8401  CCCCACTGAA CCCCTGTAAC CTATTTATTA TATAAAGAGT TTGCCTTATA
8451  AATTTACATA AAAA
```

Fig. 2 (cont'd 4)

Human
Mouse

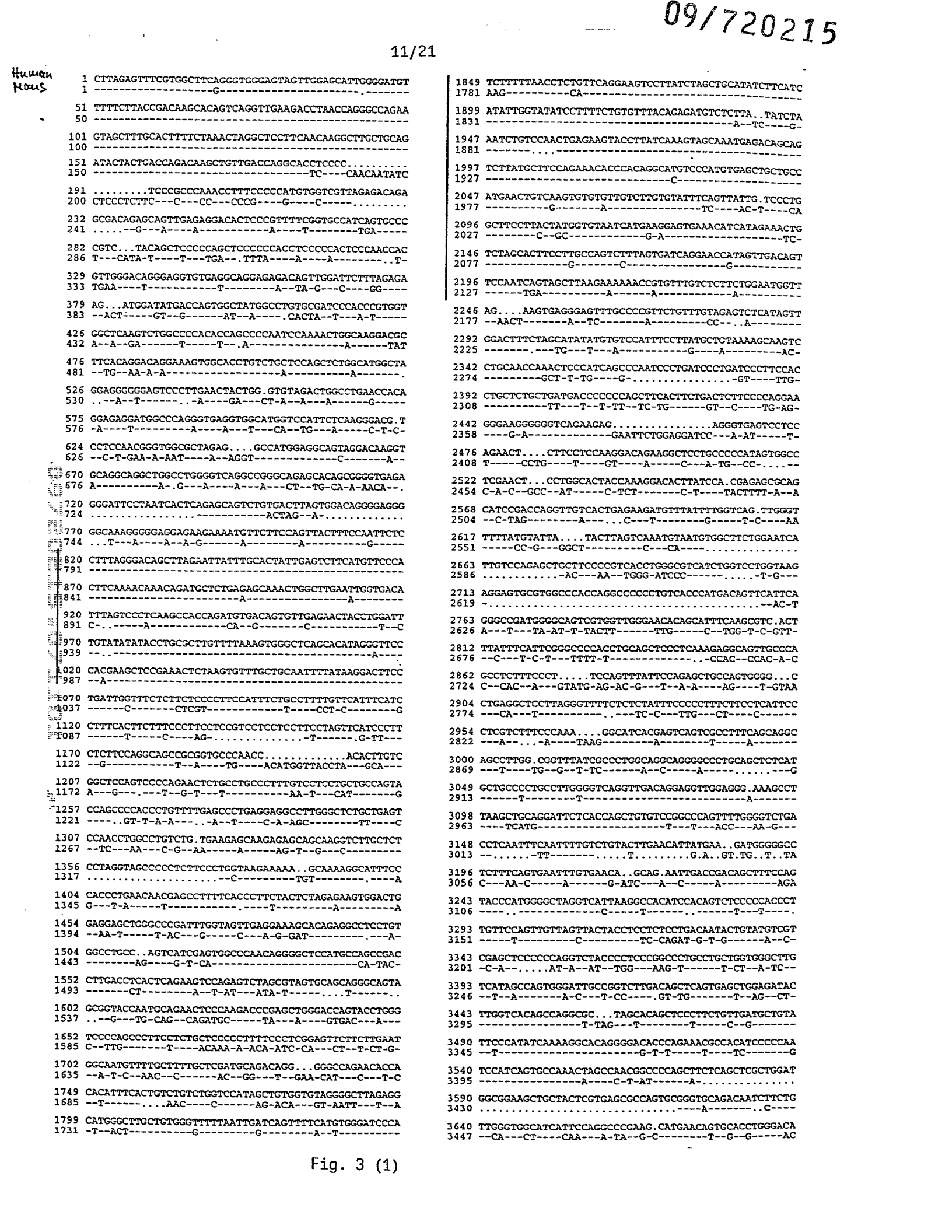

Fig. 3 (1)

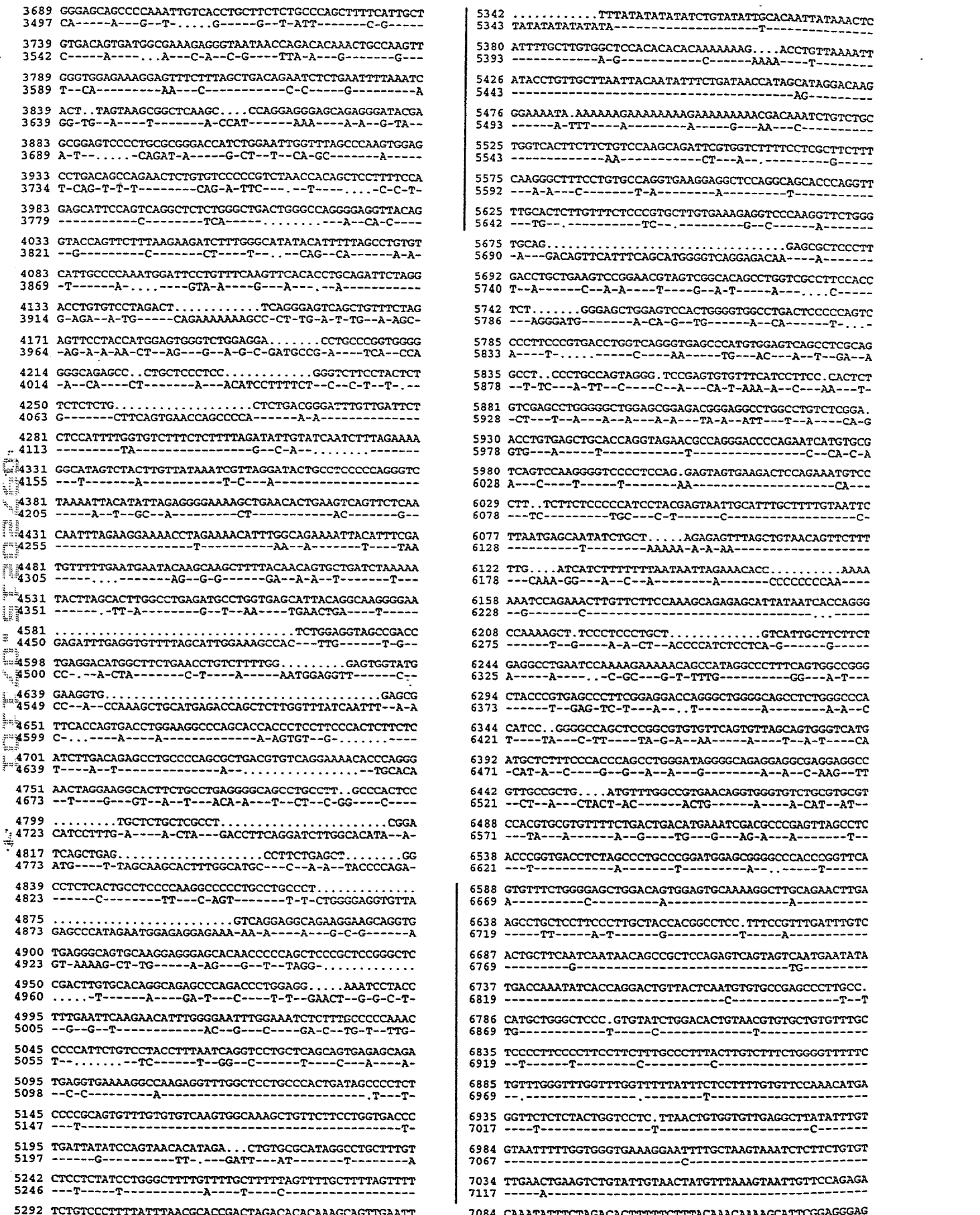

Fig. 3 (2)

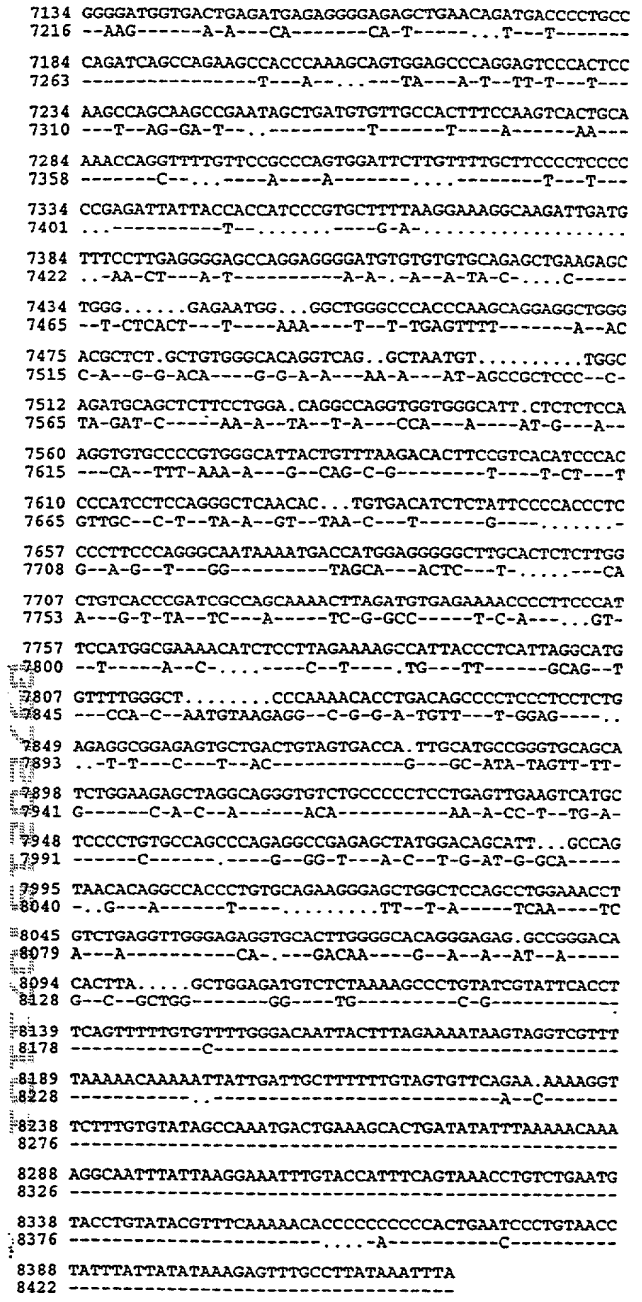

Fig. 3 (3)

dashed line: putative promoter

full line: sequence-conserved high-energy sequence

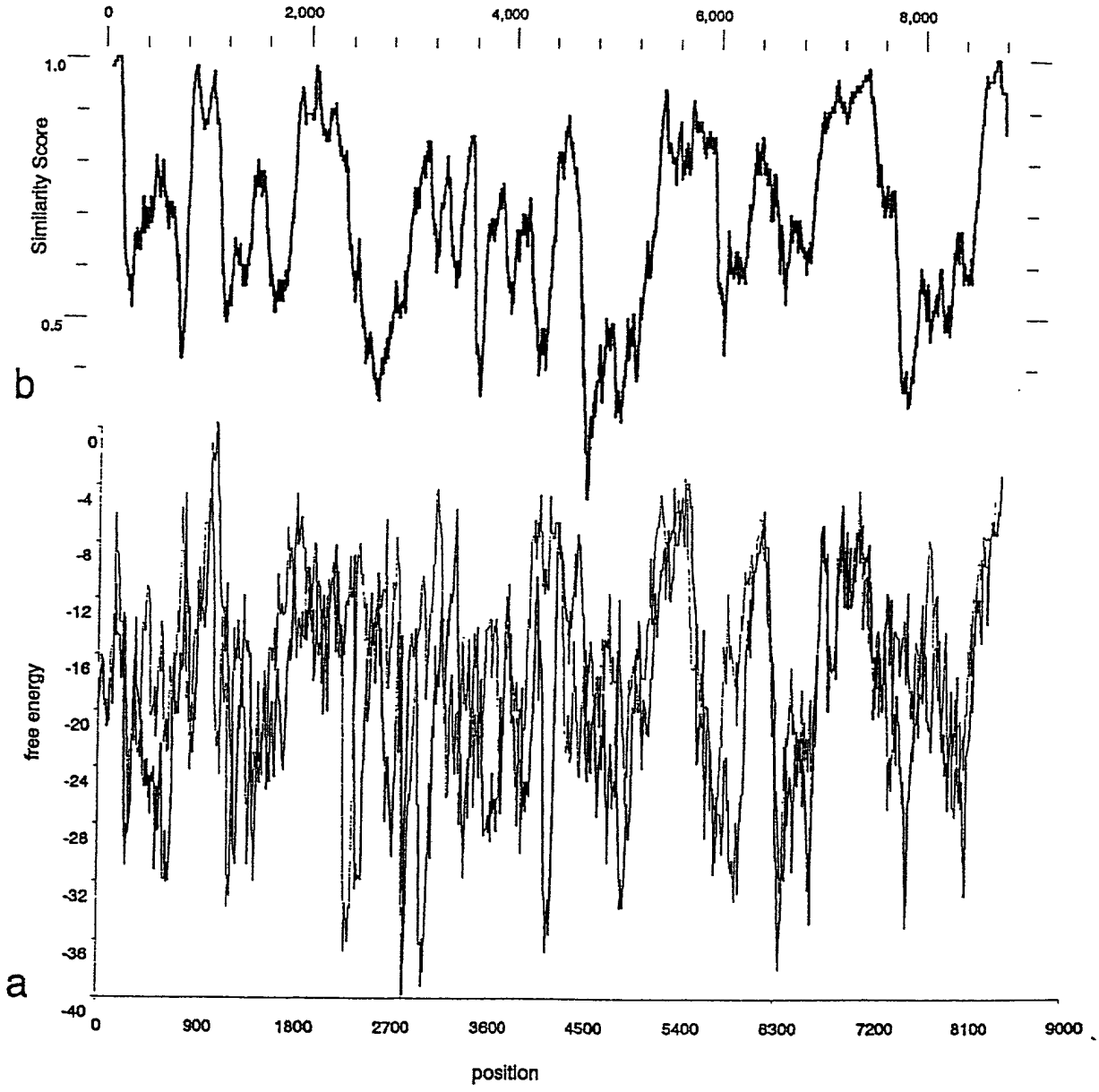

Fig. 4

black similarity 100 window

blue hinlex 10 HUMAN

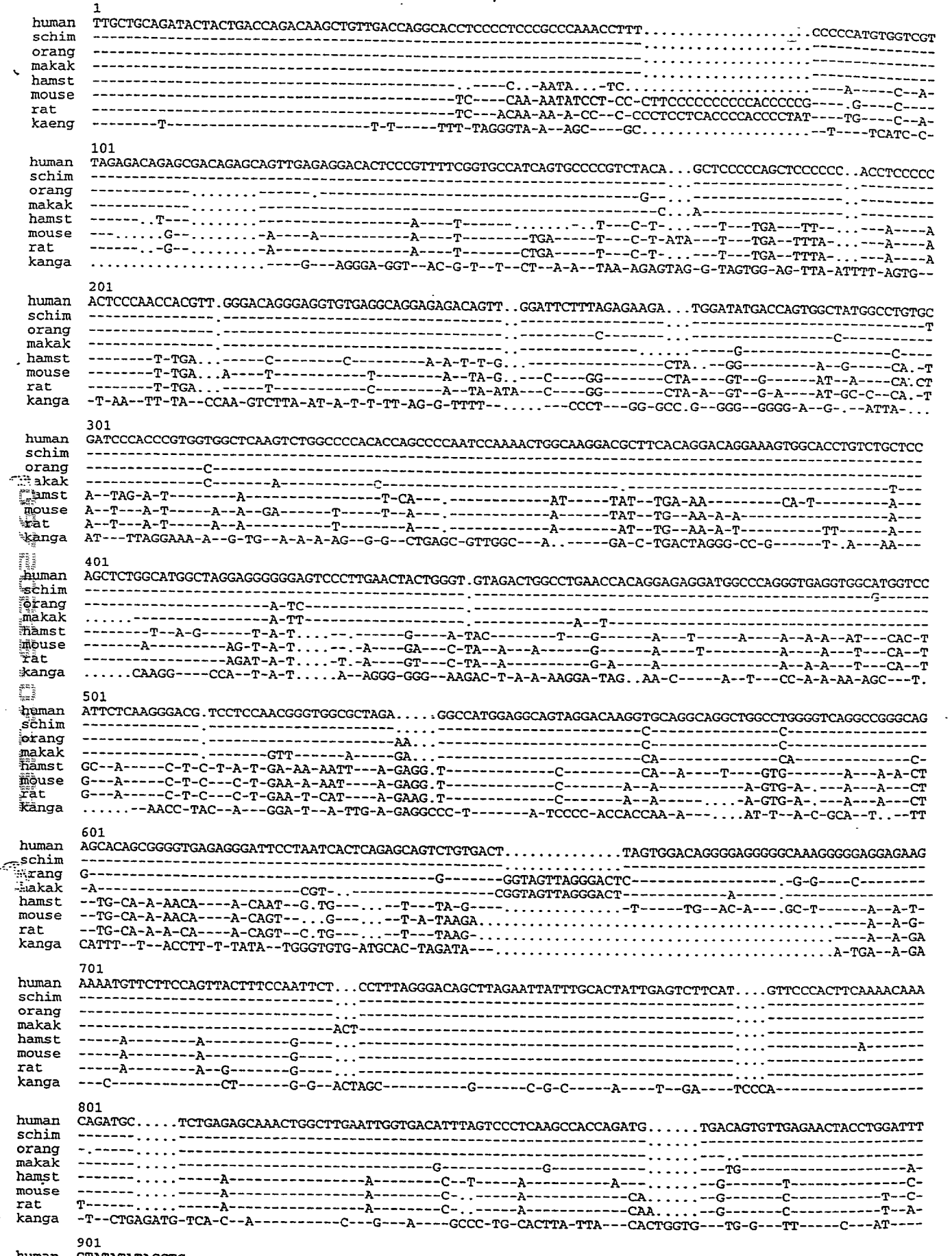

Fig. 5

Partial sequence of the non-coding RNA gene from hamster

```
   1  TTGCTGCAGA TACTACTGAC CAGACAAGCT GTTGACCAGG CACCCCCCCA
  51  ATACTCCCCC AATGTGCTCA TTAGAGATAG CAGTTGAGAG GACACTCCCA
 101  TTTTTGGTGC CCTGTCCATA GCTTCCCTGA CTCTTCCACC ACCCCAACTC
 151  CCAATCTGAG GGACCGGGAG GTGCGAGGCA GGAAAAATAT TGGATTCTTT
 201  AGAGAAGACT AGAGGTGACC AGTGACTGTG GCCCAGTAAT TAGAACTGTG
 251  GTGGCACAAG TCTGGCCCCA CATCCACCCA ATCCAAAACT GATAAGGATA
 301  TTTTGAAAAA CAGGAAAGCA GTACCTGTCT GATCCAGCTC TGGTATAGGT
 351  AGGAGTGAGT CCTGAACTGC TGGATTACAG ACTGGCTTGA GCCACAGAAG
 401  ATGATGGACC AGAGTAAAGT ATCATCACCT GCTCACAAGG CATGCTTCAC
 451  TAGAGAATAA TTCTAAAGAG GTGCCATGGA GGCAGCAGGA CAAGGCACAA
 501  GCAGTCTGGG TGGGGGTCAA GCCAGACCTA GTGCCACAGA ACAAGAGAGC
 551  AATCTGTGAC TAGTAGTTAG GGACTTTGTG GATGGGACAA GGGGCATGGG
 601  GGAAGAAATG AAAATATTCT TCCAATTACT TTCCAGTTCT CCTTTAGGGA
 651  CAGCTTAGAA TTATTTGCAC TATTGAGTCT TCATGTTCCC ACTTAAAAAC
 701  AAACAGATGC TCTGAAAGCA AACTGGCTTG AAATGGTGAC ACTTTGTCCC
 751  ACAAGCCACC AAATGTGGCA GTGTTTAGAA CTACCTGGAT CTGTATATAC
 801  CTG
```

Fig. 5a

Partial sequence of the non-coding RNA gene from kangaroo

```
  1  TTGCTGCATA TACTACTGAC CAGACAAGCT GTTTATCAGG CTTTTTAGGG
 51  TACACCAGCA CCTGCCCTCC ATTCATCCCT GTTGGGAGAG GGATGGTGTA
101  CTGGTTGTCA CTAGAGACCT AACAGAGTAG GGTTAGTGGG AGCTTACATT
151  TTCAGTGCCA TTAACATTCT AGTCCAAGGT CTTAAATTAT TATGTTGAGG
201  GGTTTTTTTT CCCCTGAGGG GGCCGGGGGG TGGGGGGAGG GTTGATTAGA
251  TTCCTTAGGA AAGAGGGTTG AGACAGACAG CAGAGCACTG AGCAGTTGGC
301  ACTAAAGGAG ACCTTGACTA GGGGCCAGGT GGCATCATCT AATCCCAAGG
351  GGCTCCAAGT GAGTATTAGG GTGGGGGAAG ACATTATAGA AGGAATAGAA
401  ACAGGATAGC TCAGCCTAAA GAAGAGCGGT TAAAACCCTA CCCACCAGGA
451  GTTGACTTGA AAGAGGCCCC TATGGAGGAA TCCCCAACCA CCAAAAGCAA
501  TCTTGAGCTG CAGCTGCTTC ATTTAGTGGA CCTTGTGTAT ATCTGGGTGT
551  GTATGCACAT AGATAGACAG TGAGAAAGAA AACTGTTCTT CCAGTTCTTT
601  TCCAGTGCTA CTAGCTTAGG GACAGGTTAG AACTGTCTGC ACAATTGTGT
651  GATCATTCCC ATTCCCACTT CAAAACAAAC TGACTGAGAT GTTCAACAGA
701  AAACTGGCTT CAATGGGTAA CATGCCCTTG CCACTTACTT AAGACACTGG
751  TGTGATGGGG TTTTGAACTC CCTATATTTG TAGGTATCTG
```

Fig. 5b

Partial sequence of the non-coding RNA gene from makaka

```
  1  TTGCTGCAGA TACTACTGAC CAGACAAGCT GTTGACCAGG CACCTCCCCT
 51  CCCGCCCAAA CCTTTCCCCC ATGTGGTCGT TAGAGACAGA GCAGTTGAGA
101  GGACACTCCC GTTTTCGGTG CCATCAGTGC CCCGTCTACC ACTCCCCCAG
151  CTCCCCCCAC CTCCCCCACT CCCAACCACG TTGGGACAGG GAGGTGTGAG
201  GCAGGAGAGA CAGTTGGATT CTTTAGAGAT GGATGTGACC AGTGGCTATG
251  GCCCGTGCGA TCCCACCCGT GGCGGCTCAA ATCTGGCCCC ACCCCAGCCC
301  CAATCCAAAA CTGGCAAGGA CGCTTCACAG GACAGGAAAG TGGCACCTGT
351  CTGTTCCGGC ATGGCTAGGA GGGAGTTGTC CCTTGAACTA CTGGGTGTAG
401  ACTGGCCTAA ATCACAGGAG AGGATGGCCC AGGGTGAGGT GGCATGGTCC
451  ATTCTCAAGG GACGTCCTCC AGTTGGTGGC ACTAGAGAGG CCATGGAGGC
501  AGTAGGACAA GGCACAGGCA GGCTGGCCCA GGGTCAGGCC GGGCCGAACA
551  CAGCGGGGTG AGAGGGATTC CTCGTCTCAG AGCAGTCTGT GACCGGTAGT
601  TAGGGACTTA GTGGACAGGG AAGGGGCAAA GGGGGAGGAG AAGAAAATGT
651  TCTTCCAGTT ACTTTCCAAT TCTACTCCTT TAGGGACAGC TTAGAATTAT
701  TTGCACTATT GAGTCTTCAT GTTCCCACTT CAAAACAAAC AGATGCTCTG
751  AGAGCAAACT GGCTTGAATT GGTGACGTTT AGTCCCTCAG GCCACCAGAT
801  GTGATGGTGT TGAGAACTAC CTGGATATGT ATATATACCT G
```

Fig. 5c

Partial sequence of the non-coding RNA gene from orangutan

```
  1  TTGCTGCAGA TACTACTGAC CAGACAAGCT GTTGACCAGG CACCTCCCCT
 51  CCCGCCCAAA CCTTTCCCCC ATGTGGTCGT TAGAGACAGA GCAGTTGAGA
101  GGACACTCCC GTTTTCGGTG CCATCAGTGC CCCGTCTGCA GCTCCCCCAG
151  CTCCCCCCAC CTCCCCCACT CCCAACCACG TTGGGACAGG GAGGTGTGAG
201  GCAGGAGAGA CAGTTGGATT CTTTCGAGAA GATGGATATG ACCAGTGGCC
251  ATGGCCTGTG CGATCCCACC CGTGGCGGCT CAAGTCTGGC CCCACACCAG
301  CCCCAATCCA AAACTGGCAA GGACGCTTCA CAGGACAGGA AAGTGGCACC
351  TGTCTGCTCC AGCTCTGGCA TGGCTAGGAG GGAGTCGTCC CTTGAACTAC
401  TGGGTGTAGA CTGGCCTGAA CCACAGGAGA GGATGGCCCA GGGTGAGGTG
451  GCATGGTCCA TTCTCAAGGG ACGTCCTCCA ACGGGTGGCG CTAGAAAGGC
501  CATGGAGGCA GTAGGACAAG GCGCAGGCAG GCTGGCCCGG GGTCAGGCCG
551  GGCAGGGCAC AGCGGGGTGA GAGGGATTCC TAATCACTCA GAGCAGTGTG
601  TGACTGGTAG TTAGGGACTC AGTGGACAGG GGAGGGGCGA GGGGGCAGGA
651  GAAGAAAATG TTCTTCCAGT TACTTTCCAA TTCTCCTTTA GGGACAGCTT
701  AGAATTATTT GCACTATTGA GTCTTCATGT TCCCACTTCA AAACAAACGA
751  TGCTCTGAGA GCAAACTGGC TTGAATTGGT GACATTTAGT CCCTCAAGCC
801  ACCAGATGTG AGTGTTGAGA ACTACCTGGA TTTGTATATA TACCTG
```

Fig. 5d

Partial sequence of the non-coding RNA gene from rat

```
  1  TTGCTGCAGA TACTACTGAC CAGACAAGCT GTTGACCAGG CACTCCCCAC
 51  AACAACAACC CCCTCCCTCC TCACCCCACC CCTATCCCCT GTGTGCTCAT
101  TAGAGAGGGC AATTGAGAGG ACACTCCCAT TTTTGGTGCC ACTGATGCCC
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251  TATAGAGTTG GCAAGTGATT GCGCCCCAGT AATTCCAACT GTGGTAGCAC
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601  GTAGTTAAGG GGGAAGAAAG AAAAATATTC TTCCAATTGC TTTCCAGTTC
651  TCCTTTAGGG ACAGCTTAGA ATTATTTGCA CTATTGAGTC TTCATGTTCC
701  CACTTCAAAA CAAATAGATG CTCTGAAAGC AAACTGGCTT GAAATGGTGA
751  CACTGTCCCA CAAGCCACCA GACAATGGCA GTGTTCAGAA CTACCTGTAT
801  ATGTATATAC CTG
```

Fig. 5e

Partial sequence of the non-coding RNA gene from chimpanzee

```
  1  TTGCTGCAGA TACTACTGAC CAGACAAGCT GTTGACCAGG CACCTCCCCT
 51  CCCGCCCAAA CCTTTCCCCC ATGTGGTCGT TAGAGACAGA GCGACAGAGC
101  AGTTGAGAGG ACACTCCCGT TTTCGGTGCC ATCAGTGCCC CGTCTACAGC
151  TCCCCCAGCT CCCCCCACCT CCCCCACTCC CAACCACGTT GGGACAGGGA
201  GGTGTGAGGC AGGAGAGACA GTTGGATTCT TTAGAGAAGA TGGATATGAC
251  CAGTGGCTAT GGCCTGTGTG ATCCCACCCG TGGTGGCTCA AGTCTGGCCC
301  CACACCAGCC CCAATCCAAA ACTGGCAAGG ACGCTTCACA GGACAGGAAA
351  GTGGCACCTG TCTGCTCCAG CTCTGGCATG GCTAGGAGGG GGGAGTCCCT
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501  AGAGGCCATG GAGGCAGTAG GACAAGGCGC AGGCAGGCTG GCCCGGGGTC
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651  ATGTTCTTCC AGTTACTTTC CAATTCTCCT TTAGGGACAG CTTAGAATTA
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751  GAGAGCAAAC TGGCTTGAAT TGGTGACATT TAGTCCCTCA AGCCACCAGA
801  TGTGACAGTG TTGAGAACTA CCTGGATTTG TATATATACC TG
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Fig. 5f

K 2912 - P 287

COMBINED DECLARATION FOR PATENT APPLICATION AND POWER OF ATTORNEY **(Includes Reference to Provisional and PCT International Applications)**	Attorney's Docket No. 012627-019

As a below named inventor, I hereby declare that:
My residence, post office address and citizenship are as stated below next to my name;
I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

MODULARLY CONSTRUCTED RNA MOLECULES HAVING TWO SEQUENCE REGION TYPES

the specification of which (check only one item below):

☐ is attached hereto.

☐ was filed as United States application
Number _____
on _____
and was amended
on _____ (if applicable).

☒ was filed as PCT international application
Number PCT/DE99/01867
on 25 June 1999
and was amended
on _____ (if applicable).

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose to the Office all information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, §1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, §119 (a)-(e) of any foreign application(s) for patent or inventor's certificate or of any PCT international application(s) designating at least one country other than the United States of America listed below and have also identified below any foreign application(s) for patent or inventor's certificate or any PCT international application(s) designating at least one country other than the United States of America filed by me on the same subject matter having a filing date before that of the application(s) of which priority is claimed:

PRIOR FOREIGN/PCT APPLICATION(S) AND ANY PRIORITY CLAIMS UNDER 35 U.S.C. §119:

COUNTRY (if PCT, indicate "PCT")	APPLICATION NUMBER	DATE OF FILING (day, month, year)	PRIORITY CLAIMED UNDER 35 U.S.C. §119
DE	198 28 624.4	26 June 1998	X Yes _No
			_Yes _No
			_Yes _No
			_Yes _No
			_Yes _No

I hereby claim the benefit under Title 35, United States Code § 119(e) of any United States provisional application(s) listed below.

_____ _____
(Application Number) (Filing Date)

_____ _____
(Application Number) (Filing Date)

(01/01)

COMBINED DECLARATION FOR PATENT APPLICATION AND POWER OF ATTORNEY (CONT'D) (Includes Reference to Provisional and PCT International Applications)	Attorney's Docket No. 012627-019

I hereby claim the benefit under Title 35, United States Code, §120 of any United States applications(s) or PCT international application(s) designating the United States of America that is/are listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in that/those prior application(s) in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose to the Office all information known to me to be material to the patentability as defined in Title 37, Code of Federal Regulations §1.56, which became available between the filing date of the prior application(s) and the national or PCT international filing date of this application:

PRIOR U.S. APPLICATIONS OR PCT INTERNATIONAL APPLICATIONS DESIGNATING THE U.S. FOR BENEFIT UNDER 35 U.S.C. §120:

U.S. APPLICATIONS		STATUS *(check one)*		
U.S. APPLICATION NUMBER	U.S. FILING DATE	PATENTED	PENDING	ABANDONED

PCT APPLICATIONS DESIGNATING THE U.S.					
PCT APPLICATION NO.	PCT FILING DATE	U.S. APPLICATION NUMBERS ASSIGNED (if any)			

I hereby appoint the following attorneys and agent(s) to prosecute said application and to transact all business in the Patent and Trademark Office connected therewith and to file, prosecute and to transact all business in connection with international applications directed to said invention:

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Alan E. Kopecki	25,813	B. Jefferson Boggs, Jr.	32,344	Kenneth B. Leffler	36,075
Regis E. Slutter	26,999	William H. Benz	25,952	Fred W. Hathaway	32,236
Samuel C. Miller, III	27,360	Peter K. Skiff	31,917	Wendi L. Weinstein	34,456
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George A. Hovanec, Jr.	28,223	Matthew L. Schneider	32,814		
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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

FULL NAME OF SOLE OR FIRST INVENTOR Annemarie POUSTKA	SIGNATURE	DATE 15.3.01
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POST OFFICE ADDRESS Werderstrasse 36, D-69120 Heidelberg, DE		
FULL NAME OF SECOND JOINT INVENTOR, IF ANY Johannes COY	SIGNATURE	DATE 15.3.01
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POST OFFICE ADDRESS In den schwarzen Garten 1, D-63762 Gross-Ostheim, DE		
FULL NAME OF THIRD JOINT INVENTOR, IF ANY	SIGNATURE	DATE
RESIDENCE	CITIZENSHIP	
POST OFFICE ADDRESS		
FULL NAME OF FOURTH JOINT INVENTOR, IF ANY	SIGNATURE	DATE
RESIDENCE	CITIZENSHIP	
POST OFFICE ADDRESS		
FULL NAME OF FIFTH JOINT INVENTOR, IF ANY	SIGNATURE	DATE
RESIDENCE	CITIZENSHIP	
POST OFFICE ADDRESS		
FULL NAME OF SIXTH JOINT INVENTOR, IF ANY	SIGNATURE	DATE
RESIDENCE	CITIZENSHIP	
POST OFFICE ADDRESS		
FULL NAME OF SEVENTH JOINT INVENTOR, IF ANY	SIGNATURE	DATE
RESIDENCE	CITIZENSHIP	
POST OFFICE ADDRESS		
FULL NAME OF EIGHTH JOINT INVENTOR, IF ANY	SIGNATURE	DATE
RESIDENCE	CITIZENSHIP	
POST OFFICE ADDRESS		

Patent
Attorney's Docket No. 012627-019

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of	)	
	)	
Annemarie Poustka et al	)	Group Art Unit: Not yet assigned
	)	
Serial No.: 09/720,215	)	Examiner: Not yet assigned
	)	
Filed: December 22, 2000	)	**ATTENTION: BOX SEQUENCE**
	)	
For: Modularly Constructed RNA Molecules Having Two Sequence Region Types	)	

DECLARATION PURSUANT TO 37 C.F.R. §§1.821-1.825

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

I, Teresa Stanek Rea, declare as follows:

1. That the content of the paper and computer readable copies of the Sequence Listing, submitted in accordance with 37 C.F.R. §1.821(c) and (e), respectively, are the same in compliance with §1.821(f).

2. That the submission, filed in accordance with 37 C.F.R. §1.821(g)[or (h)], herein does not include new matter [or go beyond the disclosure in the international application].

3. That the substitute copy of the computer readable form, submitted in accordance with 37 C.F.R. §1.825(d), is identical to that originally filed.

I hereby declare that all statements made herein of my own knowledge are true and that all statements were made on information and belief and are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

7/11/01
Date

Teresa Stanek Rea
Registration No. 30,427

SEQUENCE LISTING

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SEQUENCE PROTOCOL

(1) GENERAL INDICATIONS:

(i) APPLICANT:
(A) NAME: Deutsches Krebsforschungszentrum
(B) STREET: Im Neuenheimer Feld 280
(C) TOWN: Heidelberg
(E) COUNTRY: Germany
(F) POSTAl CODE: 69120

(ii) TITLE OF THE INVENTION: Modularly Constructed RNA Molecules Having Two Sequence Region Types

(iii) NUMBER OF SEQUENCES: 8

(iv) COMPUTER-READABLE VERSION:
(A) DATA CARRIER: floppy disk
(B) COMPUTER: IBM PC compatible
(C) OPERATING SYSTEM: PC-DOS/MS-DOS
(D) SORTWARE: PatentIn Release #1.0, version #1.30 (EPO)

(v) DATA OF THE CURRENT APPLICATION: not yet known

(vi) DATA OF THE PRIOR APPLICATION:
APPLICATION NUMBER: DE 198 28 624.4
FILING DATE: June 26, 1998

(2) INDICATIONS AS TO ID NO: 1:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 8422 base pairs
(B) KIND: nucleotide
(C) STRAND FORM: not known
(D) TOPOLOGY: not known

(ii) KIND OF MOLECULE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 1:

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(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 8464 amino acids
(B) KIND: nucleotide
(C) STRAND FORM: not known
(D) TOPOLOGY: not known

(ii) KIND OF MOLECULE: cDNA

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CCCTCCTAAA CTTACCCCAG AGCCTCTCCC TGCCTCCTTA AGCCAGTCTG CCTGTCTTCT 4860

GGGGAGGTGT TAGAGCCCAT AGAATGGAGA GGAGAAAGAA AAGAGGAAGA GGCAGGCAGG 4920

TAGTAAAAAG GCTCTGGGAG GAAAGACAGC CTCCTAGGCT TTGCACAAGC AGGACTCAGC 4980

CCCTTGTGGG AACTAAGTGC CATCTTGGAG TTTAAGAACA TTTGGACAAG TTGCAAATGA 5040

CCTTTGCTCC TTGCTCCTCT CACCTTTTAT GGGGCCCTGC TTAGCACTGA AAGCAAATGC 5100

GCTGAAAAGG CAAAGAGGTT TGGCTCCTGC CCACTGATAG TCCTTTCCCT GCAGTGTTTG 5160

TGTGTCAAGT GGCAAAGCTG TTCTTCCTGG TGACTCTGAT TAGATCCAGT AACTTAAGAG 5220

ATTTGTATGC ATAGGTCTGC TTTGACTCTT CTATTCTGGG CTTTTGATTT GTTTTTCAGT 5280

TTTGCTTTTA GTTTTCCTAT TTTTATTTTA TGCACCAACT AGACACACAA AGCAGTTGAA 5340

TTTATATATA TATATATATA TATATATCTG TATATTTCAC AATTATAAAC TCATTTTGCT 5400

TGTGACGCCA CACACACACA AAAAGAAAAA CCTTTTAAAA TTATACCTGT TGCTTAATTA 5460

CAATATTTCT GATAACCATA GAGTAGGACA AGGGAAAAAA TTTAAAAAAA AAAAAAAAAA 5520

AAGAAAAAAC ACATCTGTCT GCTGGTCACT TCTTCAATCC AAGCAGATCT GTGATCTTTC 5580

CTCGCGTCTT TCAAAGACTT CCCTGTGCTA AGTGAAGGAA GCTCCAGGCT GCACCCAGGT 5640

TTTGTGCTTT GTTTCTCCTC TGTTGTGAAA GGGGCCCCAA GATTCTGGGT ACAGGACAGT 5700

TCATTTCAGC ATGGGGTCAG GAGACAAGAG CACTCCCTTT ACATGCTGAC GTACAGAACT 5760

TAGTGGGAAT AGCCTAGTCC CCACCTCTAG GGATGGGGAG CTAGCATGCA TGGGGGTGAC 5820

CCAACTCCCT CCACCTTTCC CTGGCCAGGA AGAGCCTGTG TACAGTAAGT CTGACAAGCT 5880

TTCCCCAGTT AGCAGGGCTC AGAGCATTTA AAAACCCTCC AAACTTTGCT GAGTCTAGGG 5940

ACTAGAGAGA AGATAGAAGA TTTGGTCTAT CTCCAAGGTG TGTAAGCTGT ACCAGGTAGA 6000

ATGCCAGGGA CCCCAGAACC ACATCCAACA GCCCAATGGG TCTCCTCCAG AAAGTAGTGA 6060

AGACTCCAGA AACATCCCTT TCTCTTCTCC CTGCTCCCAT GAGTAACTGC ATTTGCTTTT 6120

GTAATCCTTA ATGAGCATTA TCTGCTAAAA AAAAAAAATT AGCTGTAACA GTTCTTTTTG 6180

CAAAAGGATC ATTCTTAAAT AATTAAAAAC ACCCCCCCCC CAAAAAAAAG TCCAGAACCT 6240

TGTTCTTCCA AAGCAGAGAG CATTATAATC AGGGCCAAAA TCTGTCCCAC ACCTCTACCC 6300

CATCTCCTCA TGATTGCTGC TTCTAAGGCC AGAATACAGC AAAGATATTT GTAGGCCCTT 6360

TGGGTGACTG GGCTACCCTT GGAGCTCTTG GAAGATGGGC TGGGGAAGCC TCTGAGACCC 6420

TATCCTAGGG CCTTGCTCTA GGGAGTAATC AGTATTAGTA GAGTGTCACA ACATTATTCC 6480

CCAGCCGGCA TGAGATGGGG GCAGAAGAAG CCAAAGGGTT GTCTCCACTG CTACTTACTT 6540

GGCCACTGAC AGGTAGGTGA CCATGTATGT CCATATGCAT GTTTTATGGC TGATGTGAGA 6600

TCAGCACCCA AGTTAGCTTC ACCTGGTGAC CTCTAACCCT GCCTGGATGG AGCAGGCCAC 6660

CTGGTTCAAT GTTTCTGGGC AGCTGGACAA TGGAGTGCAA AAGGCTTACA GAACTTGAAG 6720

CCTTTTCCTT ACTTTGCTAG CACGGCCTCC TTTTCCATTT GATTTGTCAC TGCTTCAGTC 6780

AATAACAGCC GCTCCAGAGT CAGTAGTTGA TGAATATATG ACCAAATATC ACCAGGACTG 6840

TTACTCAACG TGTGCCGAGC CCTTTCCTTG TGCTGGGCTC CCTGTGTACC TGGACACTGT 6900

AATGTGTGCT GTGTTTGCTC TCCTTCCTCT TCCTTCCTTG CCCTTTCCTT GTCTTTCTGG 6960

GGTTTTTCTG TTGGGTTTGG TTTGGTTTTA TTTTTCCTTT TGTGTTCCAA ACATGAGGTT 7020

TTCTCTACTG GTCCTCTTTA ACTGTGGTGT TGAGGCTTCT ATTTGTGTAA TTTTTGGTGG 7080

GTGAAAGGAA CTTTGCTAAG TAAATCTCTT CTGTGTTTGA AATGAAGTCT GTATTGTAAC 7140

TATGTTTAAA GTAATTGTTC CAGAGACAAA TGCTTCTAGG TACATTTTCA TTACAAACAA 7200

AGCATTTGAA GGGAGGGAAG TGGTGAATAA GACAAGAGGG GCAATCTGAA TTGATCCCTG 7260

CCCAGATCAG CCAGAAGCTA CCAAAAGTTA AGCACTGGTT TTCCATTCCA AGTCAAGAGA 7320

CTGAAGCTGA TGTTTTGCCA TTTTCAAAGT CAAAGCAAAA CCAGCTTTTC CACCCAATGG 7380

ATTCTTTGCT TCTCCTTCCC AGATTATTAC TACTGCTGTA ATAATCTAGG AGTGCCAGGA 7440

GGGAAAGGAG TATTAACACA GAGCTGTGCT CACTGAGTAT GGAAAGGCTT GGTCTGAGTT 7500

TTCAGGAGGA TGACCCACTG TGGACATGGG GAGAAGACAG AAGATAAATT AGCCGCTCCC 7560

TGCCTAAGAT ACCTCTTAAT AGATAAGTCA AGGCCATGGA CATTATTGTC TACAAGGCAT 7620

GTTTCAAAGA CATGACCAGT CAGGACACTT CTGTCATACT CCATGTTGCC CCCTAGTACA 7680

CAGTACTAAT CTGATATCTC TGTTCCCGCC ATGCCTGGGG GATAAAATGA TAGCAGAGAC 7740

TCCTTTCCTT CAATGTGATC TAATTCCCAA CAAAATCTGG GCCTGAGATA CCACCTGTTT 7800

CTATGGCAAA CATCCTCAGT AAAGTGTTAT TCTCATTGCA GATTGTTCCA GCCTAATGTA 7860

AGAGGAACAG AGCAGTGTTC CCTTGGAGCC TCATGTGGAC AGTTCTACCT GTAGTGACCA 7920

GTTGGCTATA GTAGTTATTA GCTGGAACAA CCAGACAGGG TACATGCCCC CTCCAAAATC 7980

CATGTTGTAC TCCCCTCTGC CAGCCAGGGG GGGTGAGATC TGTAGAATAG TGCAGCCAGT 8040

GACAAGCCAC CTTGTGTTTG TCACCAGCTC AAAAACTCAT CTAAGGTTGG GAGCAGGCAG 8100

ACAAGGCAGA GAGAAAGATC CAGGACAGAC CTAGCTGGGC TGGAGGGGTC TTGAAAAGCC 8160

CTCTGTCGTA TTCACCTTCA GTTTTTGTGC TTTGGGACAA TTACTTTAGA AAATAAGTAG 8220

GTCGTTTTAA AAACAAAATA TTGATTGCTT TTTTGTAGTG TTCAAAACAA AAGGTTCTTT 8280

GTGTATAGCC AAATGACTGA AAGCACTGAT ATATTTAAAA ACAAAAGGCA ATTTATTAAG 8340

GAAATTTGTA CCATTTCAGT AAACCTGTCT GAATGTACCT GTATACGTTT CAAAAACACA 8400

CCCCACTGAA CCCCTGTAAC CTATTTATTA TATAAAGAGT TTGCCTTATA AATTTACATA 8460

AAAA 8464

(2) INDICATIONS AS TO ID NO: 3:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 803 base pairs
(B) KIND: nucleotide
(C) STRAND FORM: not known
(D) TOPOLOGY: not known

(ii) KIND OF MOLECULE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 3:

TTGCTGCAGA TACTACTGAC CAGACAAGCT GTTGACCAGG CACCCCCCCA ATACTCCCCC 60

AATGTGCTCA TTAGAGATAG CAGTTGAGAG GACACTCCCA TTTTTGGTGC CCTGTCCATA 120

GCTTCCCTGA CTCTTCCACC ACCCCAACTC CCAATCTGAG GGACCGGGAG GTGCGAGGCA 180

GGAAAAATAT TGGATTCTTT AGAGAAGACT AGAGGTGACC AGTGACTGTG GCCCAGTAAT 240

TAGAACTGTG GTGGCACAAG TCTGGCCCCA CATCCACCCA ATCCAAAACT GATAAGGATA 300

TTTTGAAAAA CAGGAAAGCA GTACCTGTCT GATCCAGCTC TGGTATAGGT AGGAGTGAGT 360

CCTGAACTGC TGGATTACAG ACTGGCTTGA GCCACAGAAG ATGATGGACC AGAGTAAAGT 420

ATCATCACCT GCTCACAAGG CATGCTTCAC TAGAGAATAA TTCTAAAGAG GTGCCATGGA 480

GGCAGCAGGA CAAGGCACAA GCAGTCTGGG TGGGGGTCAA GCCAGACCTA GTGCCACAGA 540

ACAAGAGAGC AATCTGTGAC TAGTAGTTAG GGACTTTGTG GATGGGACAA GGGGCATGGG 600

GGAAGAAATG AAAATATTCT TCCAATTACT TTCCAGTTCT CCTTTAGGGA CAGCTTAGAA 660

TTATTTGCAC TATTGAGTCT TCATGTTCCC ACTTAAAAAC AAACAGATGC TCTGAAAGCA 720

AACTGGCTTG AAATGGTGAC ACTTTGTCCC ACAAGCCACC AAATGTGGCA GTGTTTAGAA 780

CTACCTGGAT CTGTATATAC CTG 803

(2) INDICATIONS AS TO ID NO: 4:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 790 base pairs
(B) KIND: nucleotide
(C) STRAND FORM: not known
(D) TOPOLOGY: not known

(ii) KIND OF MOLECULE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 4:

TTGCTGCATA TACTACTGAC CAGACAAGCT GTTTATCAGG CTTTTTAGGG TACACCAGCA 60

CCTGCCCTCC ATTCATCCCT GTTGGGAGAG GGATGGTGTA CTGGTTGTCA CTAGAGACCT 120

AACAGAGTAG GGTTAGTGGG AGCTTACATT TTCAGTGCCA TTAACATTCT AGTCCAAGGT 180

CTTAAATTAT TATGTTGAGG GGTTTTTTTT CCCCTGAGGG GGCCGGGGGG TGGGGGGAGG 240

GTTGATTAGA TTCCTTAGGA AAGAGGGTTG AGACAGACAG CAGAGCACTG AGCAGTTGGC 300

ACTAAAGGAG ACCTTGACTA GGGGCCAGGT GGCATCATCT AATCCCAAGG GGCTCCAAGT 360

GAGTATTAGG GTGGGGGAAG ACATTATAGA AGGAATAGAA ACAGGATAGC TCAGCCTAAA 420

GAAGAGCGGT TAAAACCCTA CCCACCAGGA GTTGACTTGA AAGAGGCCCC TATGGAGGAA 480

TCCCCAACCA CCAAAAGCAA TCTTGAGCTG CAGCTGCTTC ATTTAGTGGA CCTTGTGTAT 540

ATCTGGGTGT GTATGCACAT AGATAGACAG TGAGAAAGAA AACTGTTCTT CCAGTTCTTT 600

TCCAGTGCTA CTAGCTTAGG GACAGGTTAG AACTGTCTGC ACAATTGTGT GATCATTCCC 660

ATTCCCACTT CAAAACAAAC TGACTGAGAT GTTCAACAGA AAACTGGCTT CAATGGGTAA 720

CATGCCCTTG CCACTTACTT AAGACACTGG TGTGATGGGG TTTTGAACTC CCTATATTTG 780

TAGGTATCTG 790

(2) INDICATIONS AS TO ID NO: 5:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 841 base pairs
(B) KIND: nucleotide
(C) STRAND FORM: not known
(D) TOPOLOGY: not known

(ii) KIND OF MOLECULE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 5:

TTGCTGCAGA TACTACTGAC CAGACAAGCT GTTGACCAGG CACCTCCCCT CCCGCCCAAA 60

CCTTTCCCCC ATGTGGTCGT TAGAGACAGA GCAGTTGAGA GGACACTCCC GTTTTCGGTG 120

CCATCAGTGC CCCGTCTACC ACTCCCCCAG CTCCCCCCAC CTCCCCCACT CCCAACCACG 180

TTGGGACAGG GAGGTGTGAG GCAGGAGAGA CAGTTGGATT CTTTAGAGAT GGATGTGACC 240

AGTGGCTATG GCCCGTGCGA TCCCACCCGT GGCGGCTCAA ATCTGGCCCC ACCCCAGCCC 300

CAATCCAAAA CTGGCAAGGA CGCTTCACAG GACAGGAAAG TGGCACCTGT CTGTTCCGGC 360

ATGGCTAGGA GGGAGTTGTC CCTTGAACTA CTGGGTGTAG ACTGGCCTAA ATCACAGGAG 420

AGGATGGCCC AGGGTGAGGT GGCATGGTCC ATTCTCAAGG GACGTCCTCC AGTTGGTGGC 480

ACTAGAGAGG CCATGGAGGC AGTAGGACAA GGCACAGGCA GGCTGGCCCA GGGTCAGGCC 540

GGGCCGAACA CAGCGGGGTG AGAGGGATTC CTCGTCTCAG AGCAGTCTGT GACCGGTAGT 600

TAGGGACTTA GTGGACAGGG AAGGGGCAAA GGGGGAGGAG AAGAAAATGT TCTTCCAGTT 660

ACTTTCCAAT TCTACTCCTT TAGGGACAGC TTAGAATTAT TTGCACTATT GAGTCTTCAT 720

GTTCCCACTT CAAAACAAAC AGATGCTCTG AGAGCAAACT GGCTTGAATT GGTGACGTTT 780

AGTCCCTCAG GCCACCAGAT GTGATGGTGT TGAGAACTAC CTGGATATGT ATATATACCT 840

G 841

(2) INDICATIONS AS TO ID NO: 6:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 846 base pairs
(B) KIND: nucleotide
(C) STRAND FORM: not known
(D) TOPOLOGY: not known

(ii) KIND OF MOLECULE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 6:

TTGCTGCAGA TACTACTGAC CAGACAAGCT GTTGACCAGG CACCTCCCCT CCCGCCCAAA 60

CCTTTCCCCC ATGTGGTCGT TAGAGACAGA GCAGTTGAGA GGACACTCCC GTTTTCGGTG 120

CCATCAGTGC CCCGTCTGCA GCTCCCCCAG CTCCCCCCAC CTCCCCCACT CCCAACCACG 180

TTGGGACAGG GAGGTGTGAG GCAGGAGAGA CAGTTGGATT CTTTCGAGAA GATGGATATG 240

ACCAGTGGCC ATGGCCTGTG CGATCCCACC CGTGGCGGCT CAAGTCTGGC CCCACACCAG 300

CCCCAATCCA AAACTGGCAA GGACGCTTCA CAGGACAGGA AAGTGGCACC TGTCTGCTCC 360

AGCTCTGGCA TGGCTAGGAG GGAGTCGTCC CTTGAACTAC TGGGTGTAGA CTGGCCTGAA 420

CCACAGGAGA GGATGGCCCA GGGTGAGGTG GCATGGTCCA TTCTCAAGGG ACGTCCTCCA 480

ACGGGTGGCG CTAGAAAGGC CATGGAGGCA GTAGGACAAG GCGCAGGCAG GCTGGCCCGG 540

GGTCAGGCCG GGCAGGGCAC AGCGGGGTGA GAGGGATTCC TAATCACTCA GAGCAGTGTG 600

TGACTGGTAG TTAGGGACTC AGTGGACAGG GGAGGGGCGA GGGGGCAGGA GAAGAAAATG 660

TTCTTCCAGT TACTTTCCAA TTCTCCTTTA GGGACAGCTT AGAATTATTT GCACTATTGA 720

GTCTTCATGT TCCCACTTCA AAACAAACGA TGCTCTGAGA GCAAACTGGC TTGAATTGGT 780

GACATTTAGT CCCTCAAGCC ACCAGATGTG AGTGTTGAGA ACTACCTGGA TTTGTATATA 840

TACCTG 846

(2) INDICATIONS AS TO ID NO: 7:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 813 base pairs
(B) KIND: nucleotide
(C) STRAND FORM: not known
(D) TOPOLOGY: not known

(ii) KIND OF MOLECULE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 7:

TTGCTGCAGA TACTACTGAC CAGACAAGCT GTTGACCAGG CACTCCCCAC AACAACAACC 60

CCCTCCCTCC TCACCCCACC CCTATCCCCT GTGTGCTCAT TAGAGAGGGC AATTGAGAGG 120

ACACTCCCAT TTTTGGTGCC ACTGATGCCC TGTCCATAGC TTCCCTGACT TTTACACCAC 180

CCCAACTCCC AATCTGAGGG ACTGGGAGGT GTGACGCAGG AGAAACTATA TAGGACTCTT 240

GGGAGAAGAC TATAGAGTTG GCAAGTGATT GCGCCCCAGT AATTCCAACT GTGGTAGCAC 300

AAGTCTGGCT CCACACCAAC CCAATCCAAA ACTGACAAGG ACATTTTGCA AAAAATGAAA 360

GTGGCATTTG TCTGATCCAG CTCTGGCATG GCTAGAGATG AGTCTTAAAC TGTTGGCTTA 420

TAAACTGGCC TGAGCAACAG AAGAGGATGG CCCAGAGTAA AGTGTCATCA TCTGTTCACA 480

AGGCATGCTC CCCTAGAAGT TCATGCTAAA GAAGTGCCAT GGAGGCAGCA GGACAAAGTA 540

CAGGCTAGGT GGAGTCAAGC CAGGCCTAGT GCCACAGAGC AAGAGAGCAG TCTCTGACTA 600

GTAGTTAAGG GGGAAGAAAG AAAAATATTC TTCCAATTGC TTTCCAGTTC TCCTTTAGGG 660

ACAGCTTAGA ATTATTTGCA CTATTGAGTC TTCATGTTCC CACTTCAAAA CAAATAGATG 720

CTCTGAAAGC AAACTGGCTT GAAATGGTGA CACTGTCCCA CAAGCCACCA GACAATGGCA 780

GTGTTCAGAA CTACCTGTAT ATGTATATAC CTG 813

(2) INDICATIONS AS TO ID NO: 8:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 842 base pairs
(B) KIND: nucleotide
(C) STRAND FORM: not known
(D) TOPOLOGY: not known

(ii) KIND OF MOLECULE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 8:

TTGCTGCAGA TACTACTGAC CAGACAAGCT GTTGACCAGG CACCTCCCCT CCCGCCCAAA 60

CCTTTCCCCC ATGTGGTCGT TAGAGACAGA GCGACAGAGC AGTTGAGAGG ACACTCCCGT 120

TTTCGGTGCC ATCAGTGCCC CGTCTACAGC TCCCCCAGCT CCCCCCACCT CCCCCACTCC 180

CAACCACGTT GGGACAGGGA GGTGTGAGGC AGGAGAGACA GTTGGATTCT TTAGAGAAGA 240

TGGATATGAC CAGTGGCTAT GGCCTGTGTG ATCCCACCCG TGGTGGCTCA AGTCTGGCCC 300

CACACCAGCC CCAATCCAAA ACTGGCAAGG ACGCTTCACA GGACAGGAAA GTGGCACCTG 360

TCTGCTCCAG CTCTGGCATG GCTAGGAGGG GGGAGTCCCT TGAACTACTG GGTGTAGACT 420

GGCCTGAACC ACAGGAGAGG ATGGCCCAGG GTGAGGTGGC GTGGTCCATT CTCAAGGGAC 480

GTCCTCCAAC GGGTGGCGCT AGAGGCCATG GAGGCAGTAG GACAAGGCGC AGGCAGGCTG 540

GCCCGGGGTC AGGCCGGGCA GAGCACAGCG GGGTGAGAGG GATTCCTAAT CACTCAGAGC 600

AGTCTGTGAC TTAGTGGACA GGGGAGGGGG CAAAGGGGGA GGAGAAGAAA ATGTTCTTCC 660

AGTTACTTTC CAATTCTCCT TTAGGGACAG CTTAGAATTA TTTGCACTAT TGAGTCTTCA 720

TGTTCCCACT TCAAAACAAA CAGATGCTCT GAGAGCAAAC TGGCTTGAAT TGGTGACATT 780

TAGTCCCTCA AGCCACCAGA TGTGACAGTG TTGAGAACTA CCTGGATTTG TATATATACC 840

TG 842